Medical Genetics

Volume I
Basic Genetics

Part XI
Developmental Genetics

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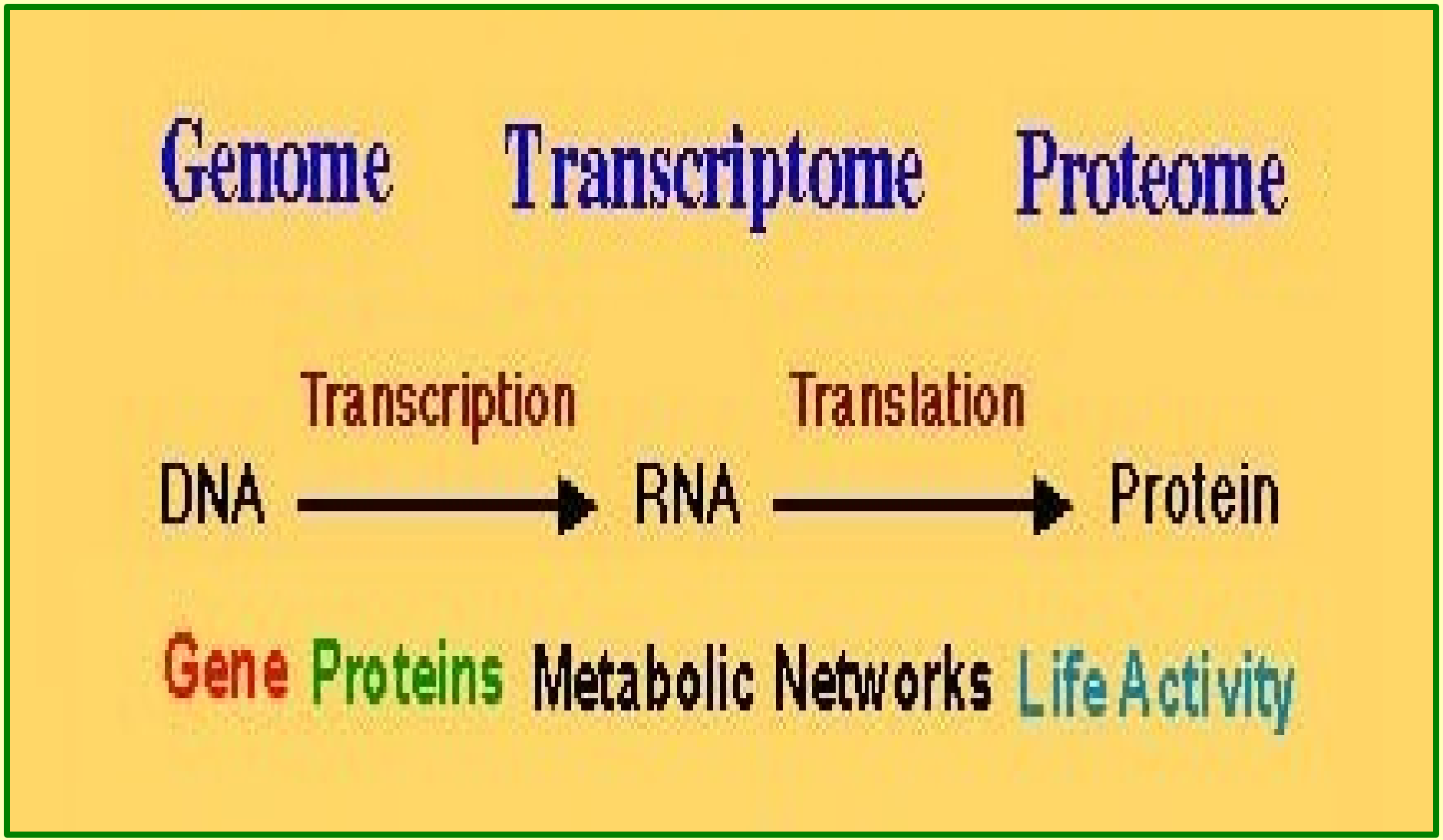
Spectrum of Medical Genetics

Basic Genetics	Clinical Genetics
Part I: Molecular Genetics Part II: Biochemical Genetics Part III: Physiological Genetics Part IIII: Cytogenetics Part V: Pathogenetics Part VI: Pharmacogenetics Part VII: Oncogenetics Part VIII: Immunogenetics Part IX: Formal Genetics Part X: Population genetics Part XI: Developmental Genetics Part XII: Genomics Part XIII: Transcriptomics Part XIV: Proteomics	Part I: Chromosomal Aberrations Part II: Congenital Malformations Part III: Inborn Errors of Metabolism Part IV: Mitochondrial Disorders Part V: Genetic Systemic Syndrome Part VI: Genetic Diseases of The Nervous system Part VII: Genetic Diseases of The Endocrinal system Part VIII: Genetic Diseases of The Cardio-Vascular system Part IX: Genetic Diseases of The Respiratory system Part X: Genetic Diseases of The Gastro-Intestinal system Part XI: Genetic Diseases of The Urinary system Part XII: Genetic Diseases of The Muscular system Part XIII: Genetic Diseases of The Skeletal system Part XIV: Genetic Diseases of The Blood system Part XV: Genetic Diseases of The Immunity system Part XVI: Genetic Diseases of The Male Genital system Part XVII: Genetic Diseases of The Female Genital system Part XVIII: Genetic Diseases of The Ocular system Part XIX: Genetic Diseases of The Auditory system Part XX: Genetic Diseases of The Skin Part XXI: Genetic Psychiatric Disorders
Diagnostic Genetics	**Therapeutic Genetics**
Part I: Molecular Diagnostic Techniques Part II: Cytogenetic Diagnostic Techniques Part III: Biochemical Diagnostic techniques Part IV: Prenatal Diagnosis Part V: Pre-Implantation Diagnosis Part VI: Per-Symptomatic Diagnosis Part VII: Conventional Diagnostic Techniques	Part I: Pharmacologic Therapy Part II: Nutritional Therapy Part III: Replacement Therapy Part IV: Transplantation Therapy Part V: Stem Cell Therapy Part VI: Surgical Intervention Part VII: Genetic Therapy Part VIII: Fetal Therapy Part IX: Conventional Therapy
Prophylactic Genetics	**Applied Genetics**
Part I: Pre-Conception Prophylaxis Part II: Pre-Natal Prophylaxis Part III: Pre-Symptomatic Prophylaxis	Part I: Forensic Genetics Part II: Genetic Counseling Part III: Genetic Screening Part IV: Genetic Engineering Part V: Eugenics

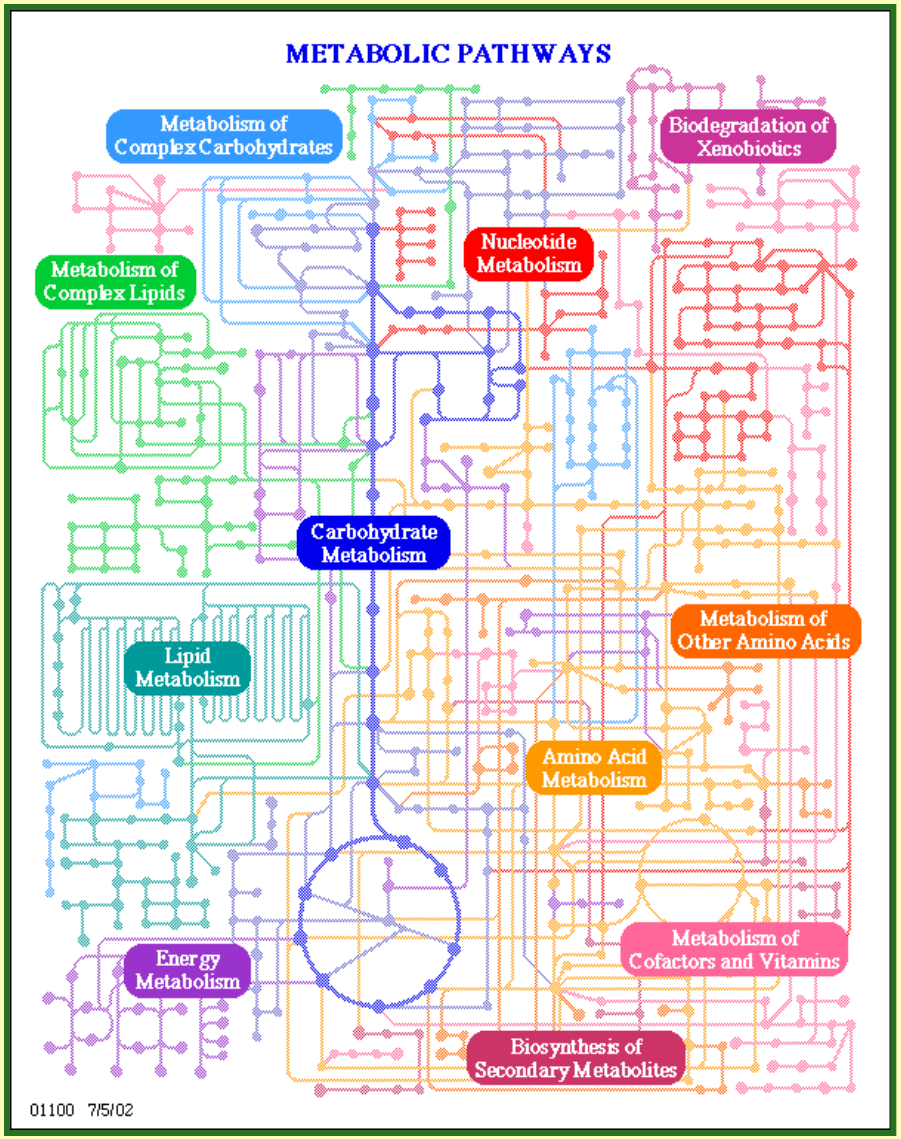
Dogma of Molecular Biology

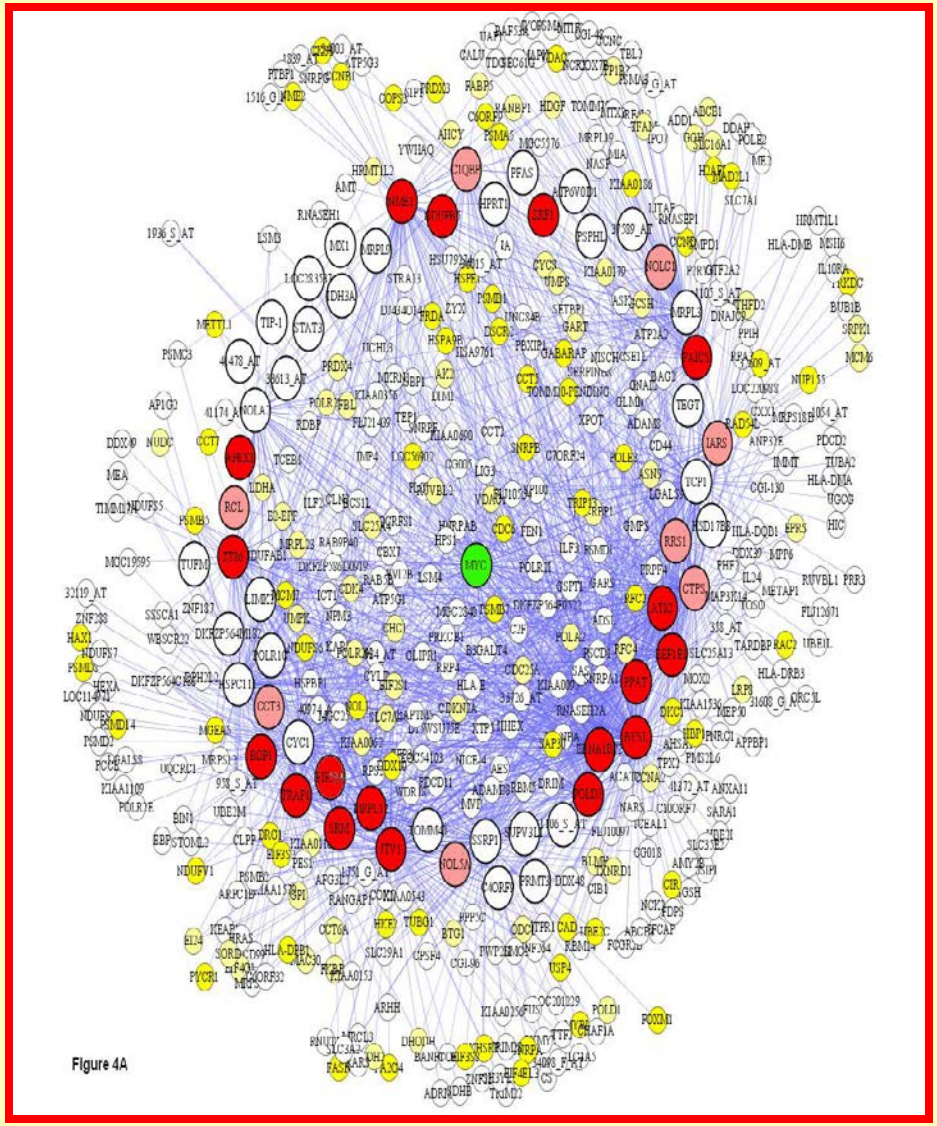
Relation Between The genetic Material and Life Activities

Life Activities at The Molecular level



The Concept Of Metabolic Networks





Developmental genetics is a branch of basic genetics concerned with studying genetic control of development of living creatures from a single cell, fertilized egg stage, to fully developed organism. It comprises the study of all aspects of development including genetic regulations exerted by the genome and mediated by the proteome all through different consequent stages of development, as well as non-genetic effects exerted by exogenous environmental factors on development.

Genetic control of development is very complex. It entails the participation of large numbers of master genes that guarantee proper initiation and progression of the different consequent and divergent stages of development according to the genetically-determined predefined profile of the developing organism, similar numbers of regulatory genes that control the meticulous harmony between exceedingly large numbers of differentially activated and

Periodic Table of Human Developmental Factors

The human developmental factors listed in the table include ligands and non-receptor, extracellular regulators of the major signaling pathways involved in Developmental Biology. The molecules are presented in a tabular format and color-coded according to family membership or regulatory activity. The information presented was obtained from standard PubMed sources. Due to space constraints, this table does not include all possible modulators of the represented signaling pathways and should not be considered definitive nor comprehensive.

Key to entries (example): 8* — Note Number (See Notes section below for additional information); Structure; 13-15 — Observed Mature Molecular Weight (kDa); 100 — % Amino Acid Identity between mouse & human; Activin A — Abbreviated Full Name; Inhibin β_A chain — Complete Name; EDF — Alternate Name; ALK-1, -2, -4; Act RIIA, RIIB; Endoglin; TGF-β RIII — Receptors (or in the case of Regulators, Ligands)

No.	Factor	Complete Name
1*	Shh	Sonic Hedgehog
2*	Notch-1-4	Neurogenic Locus Notch Homolog Protein
3*	BMP-2	Bone Morphogenetic Protein 2
4*	TGF-β1	Transforming Growth Factor beta 1
5*	Ihh	Indian Hedgehog
6*	Jagged 1	Jagged 1
7*	FGF acidic	Fibroblast Growth Factor acidic
8*	Activin A	Inhibin β_A chain
9*	Nodal	Nodal
10	GDF-5	Growth Differentiation Factor 5
11*	GDF-1	Growth Differentiation Factor 1
12*	BMP-4	Bone Morphogenetic Protein 4
13*	TGF-β2	Transforming Growth Factor beta 2
14*	Dhh	Desert Hedgehog
15	Jagged 2	Jagged 2
16	FGF basic	Fibroblast Growth Factor basic
17	Wnt-1	Wingless/Int-1 type Protein 1
18	Wnt-2	Wingless/Int-1 type Protein 2
19	Wnt-2b	Wingless/Int-1 type Protein 2b
20	Wnt-3	Wingless/Int-1 type Protein 3
21*	Wnt-3a	Wingless/Int-1 type Protein 3a
22	GDNF	Glial cell-derived Neurotrophic Factor
23*	Activin B	Inhibin β_B chain
24*	GDF-8	Growth Differentiation Factor 8
25	GDF-6	Growth Differentiation Factor 6
26*	GDF-3	Growth Differentiation Factor 3
27	BMP-5	Bone Morphogenetic Protein 5
28*	TGF-β3	Transforming Growth Factor beta 3
29*	PDGF-A	Platelet-derived Growth Factor A
30*	DLL1	Delta-like 1
31	FGF-3	Fibroblast Growth Factor 3
32	FGF-4	Fibroblast Growth Factor 4
33	FGF-8a	Fibroblast Growth Factor 8a
34	FGF-9	Fibroblast Growth Factor 9
35*	FGF-19	Fibroblast Growth Factor 19
36	Wnt-4	Wingless/Int-1 type Protein 4
37	Wnt-5a	Wingless/Int-1 type Protein 5a
38	Wnt-5b	Wingless/Int-1 type Protein 5b
39	Wnt-6	Wingless/Int-1 type Protein 6
40	Wnt-7a	Wingless/Int-1 type Protein 7a
41	Neurturin	Neurturin
42*	Activin C	Inhibin β_C chain
43	GDF-11	Growth Differentiation Factor 11
44	GDF-7	Growth Differentiation Factor 7
45*	BMP-15	Bone Morphogenetic Protein 15
46	BMP-6	Bone Morphogenetic Protein 6
47*	MIS	Müllerian Inhibiting Substance
48*	PDGF-B	Platelet-derived Growth Factor B
49*	DLL3	Delta-like 3
50	FGF-7	Fibroblast Growth Factor 7
51	FGF-5	Fibroblast Growth Factor 5
52	FGF-17	Fibroblast Growth Factor 17
53	FGF-16	Fibroblast Growth Factor 16
54	FGF-21	Fibroblast Growth Factor 21
55	Wnt-7b	Wingless/Int-1 type Protein 7b
56	Wnt-8a	Wingless/Int-1 type Protein 8a
57*	Wnt-8b	Wingless/Int-1 type Protein 8b
58*	Wnt-9a	Wingless/Int-1 type Protein 9a
59*	Wnt-9b	Wingless/Int-1 type Protein 9b
60	Artemin	Artemin
61*	Activin E	Inhibin β_E chain
62*	BMP-3	Bone Morphogenetic Protein 3
63	BMP-9	Bone Morphogenetic Protein 9
64*	GDF-9	Growth Differentiation Factor 9
65*	BMP-7	Bone Morphogenetic Protein 7
66*	Lefty-A	Lefty-A
67*	PDGF-C	Platelet-derived Growth Factor C
68	DLL4	Delta-like 4
69	FGF-10	Fibroblast Growth Factor 10
70	FGF-6	Fibroblast Growth Factor 6
71	FGF-18	Fibroblast Growth Factor 18
72	FGF-20	Fibroblast Growth Factor 20
73*	FGF-23	Fibroblast Growth Factor 23
74*	Wnt-10a	Wingless/Int-1 type Protein 10a
75*	Wnt-10b	Wingless/Int-1 type Protein 10b
76	Wnt-11	Wingless/Int-1 type Protein 11
77*	Wnt-16b	Wingless/Int-1 type Protein 16b
78*	Norrin	Norrie Disease Protein
79	Persephin	Persephin
80*	Inhibin α	Inhibin α
81	BMP-3b	Bone Morphogenetic Protein 3b
82	BMP-10	Bone Morphogenetic Protein 10
83*	GDF-15	Growth Differentiation Factor 15
84*	BMP-8	Bone Morphogenetic Protein 8
85*	Lefty-B	Lefty-B
86*	PDGF-D	Platelet-derived Growth Factor D
87*	DNER	Delta and Notch-like EGF-related Receptor
88	FGF-22	Fibroblast Growth Factor 22

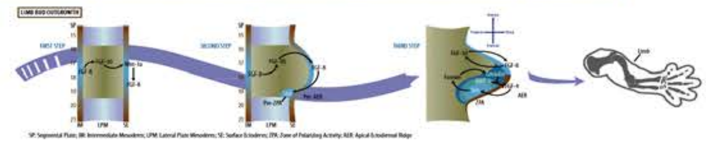
FAMILY KEY

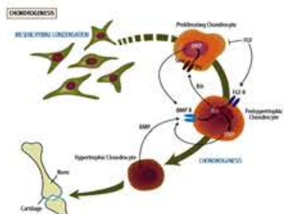
- I: Hedgehog Family
- II: PDGF Family
- III: Notch/DSL Family
- IV: FGF Family, with subfamilies (a-f)‡
- V: Wnt Family
- VI: TGF-β Family, with subfamilies (a-d)‡: GDNF, Activin, TGF-β, BMP/GDF

‡ Subfamilies grouped according to amino acid identity, with a few exceptions that are listed according to function.

STRUCTURE KEY

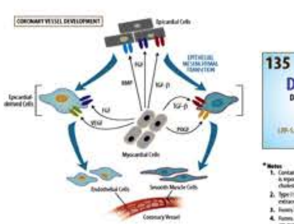
- Monomer
- Homodimer
- Heterodimer
- Single Pass Transmembrane
- GPI Linked
- Soluble





REGULATORS

No.	Regulator	Complete Name
89*	Gas1	Growth Arrest Specific
90	HIP	Hedgehog Interacting Protein
91*	MAGP-1	Microfibril-associated Glycoprotein 1
92*	MAGP-2	Microfibril-associated Glycoprotein 2
93*	FGF-BP	FGF Binding Protein
94*	Klotho	Klotho
95*	Klotho β	Klotho β
96*	Follistatin	FSH-suppressing Protein
97	FLRG	Follistatin-related Gene Protein
98*	Cripto	Cripto
99	Cryptic	Cryptic
100*	TMEFF1	Tomoregulin-1
101*	GASP-1	GDF-associated Serum Protein 1
102*	GASP-2	GDF-associated Serum Protein 2
103	Noggin	Noggin
104*	Chordin	Chordin
105	Chordin-like 1	Chordin-like 1
106	Chordin-like 2	Chordin-like 2
107*	CRIM1	Cysteine-rich Motor Neuron 1 Precursor
108*	CRIM2	Cysteine-rich Motor Neuron 2 Precursor
109*	CV-2	Crossveinless-2
110	Brorin	Brain-specific Chordin-like Protein
111*	TSG	Twisted Gastrulation
112	DAN	Differential Screening Gene Aberrant in Neuroblastoma
113	Gremlin	Gremlin
114	PRDC	Protein Related to Dan & Cerberus
115	Cerberus	Cerberus
116*	COCO	COCO
117*	SOST	Sclerostin
118*	USAG	Uterine Sensitization-associated Gene 1
119*	CTGF	Connective Tissue Growth Factor
120*	Cyr61	Cysteine-rich, Angiogenic Inducer 61
121*	NOV	Nephroblastoma Overexpressed Gene
122*	LTBP-1	Latent TGF-β Binding Protein 1
123*	LTBP-2	Latent TGF-β Binding Protein 2
124*	LTBP-3	Latent TGF-β Binding Protein 3
125*	LTBP-4	Latent TGF-β Binding Protein 4
126	Vasorin	Vasorin
127*	Decorin	Bone Proteoglycan II
128*	Biglycan	Bone/Cartilage Proteoglycan I
129	Asporin	Asporin
130*	TSK	Tsukushi
131*	SPARC	Secreted Protein, Acidic, Cysteine-rich
132*	SPP24	Secreted Phosphoprotein 24
133*	Dermatopontin	Dermatopontin
134*	CTHRC1	Collagen Triple Helix Repeat-containing Protein 1
135	Dkk-1	Dickkopf-1
136*	Dkk-2	Dickkopf-2
137*	Dkk-3	Dickkopf-3
138	Dkk-4	Dickkopf-4
139	sFRP-1	Secreted Frizzled Related Protein 1
140	sFRP-2	Secreted Frizzled Related Protein 2
141	sFRP-3	Secreted Frizzled Related Protein 3
142*	sFRP-4	Secreted Frizzled Related Protein 4
143*	sFRP-5	Secreted Frizzled Related Protein 5
144*	WIF-1	Wnt Inhibitory Factor 1
145*	R-Spondin 1	Roof Plate-specific Spondin 1
146	R-Spondin 2	Roof Plate-specific Spondin 2
147*	R-Spondin 3	Roof Plate-specific Spondin 3
148*	R-Spondin 4	Roof Plate-specific Spondin 4
149*	Myocilin	Myocilin
150*	Kremen-1	Kringle-coding Gene Marking Eye & Nose 1
151	Kremen-2	Kringle-coding Gene Marking Eye & Nose 2



Notes

suppressed structural genes which regulate the synthesis of huge numbers of proteins during stages of development. These proteins are the actual mediators of the different stages of development and can be functionally classified into the following categories:

1. Structural proteins that build the cell organelles, components of tissues and masses of organs.

2. Catalytic proteins that act as enzymes involved in constructing the innumerable numbers of metabolic networks and conducting the endless series of metabolic reactions responsible for starting and maintaining all steps and stages of development.

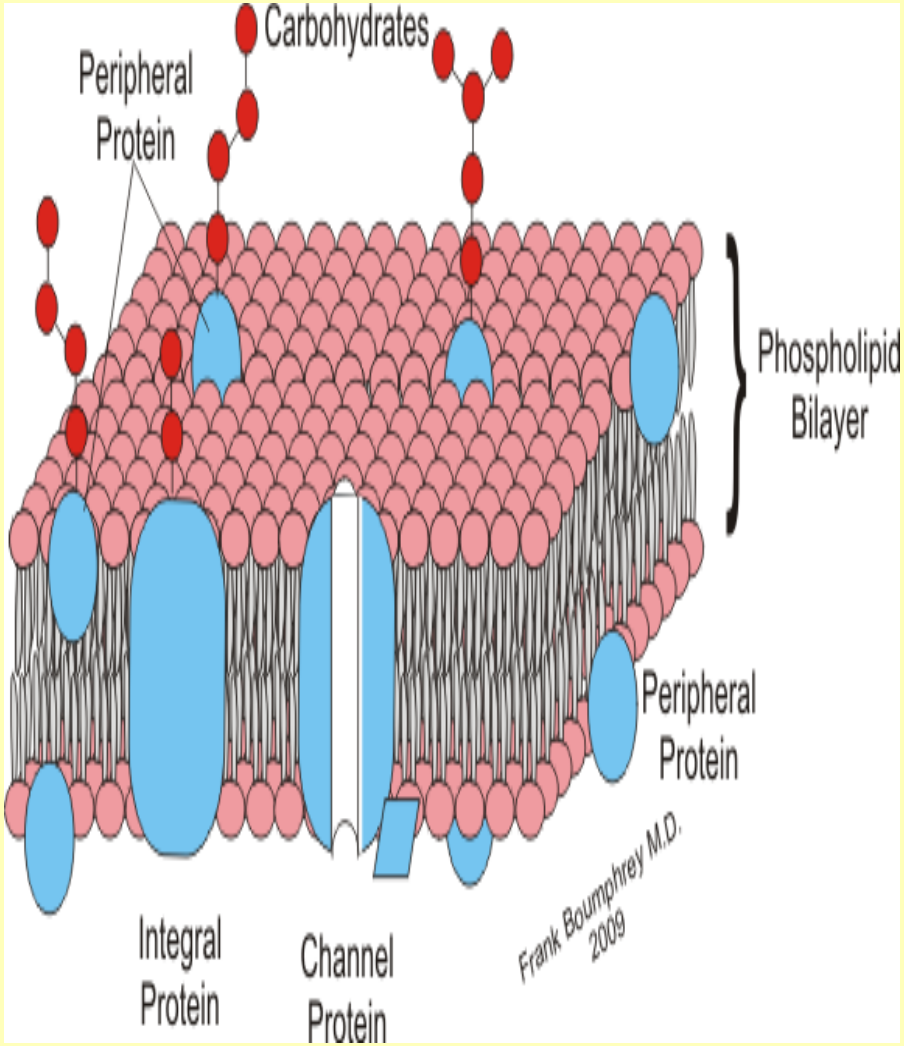
3. Signal transducing proteins that regulate synchronized activities of developmental metabolic networks. These proteins are crucial for development as they control, via the large numbers of signal transduction pathways all temporal and spatial aspects of proteome

expression in local areas of development so that proper final structures, tissues-organs and systems, are formed at proper time of development. Signal transducing proteins play pivotal roles in inter-network connections, start and termination of specific gene expression at specific times during development. Defects in these regulatory roles underlie the development of considerable fraction of congenital malformations.

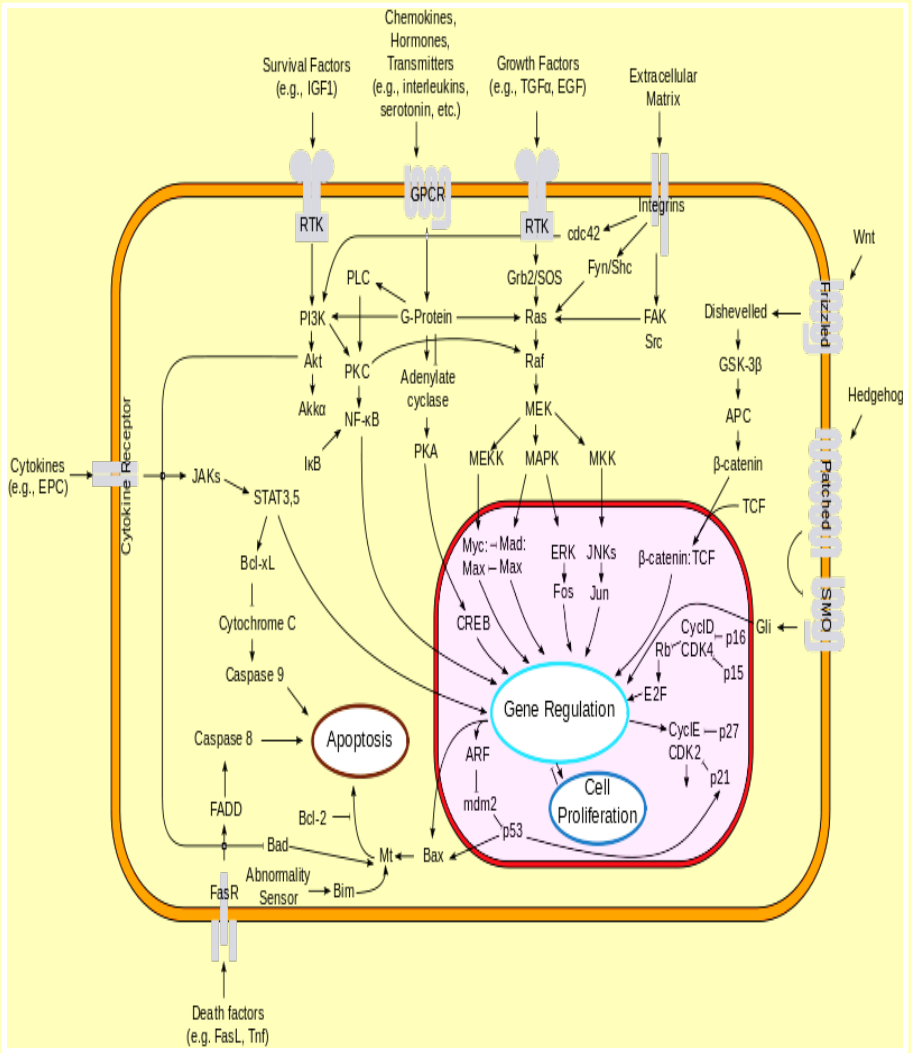
4. Regulatory proteins that play key roles in controlling all vital processes during development, as well as during postnatal life. For instance, they mediate all genetically-determined regulations of gene expression at all levels, transcriptional, post-transcriptional, mRNA transport, translation and post-translation levels. Many critical morphogenetic processes, e.g. cell migration, apoptosis, pattern and position configuration are dependent on integral functions of these regulatory proteins.

Proteins

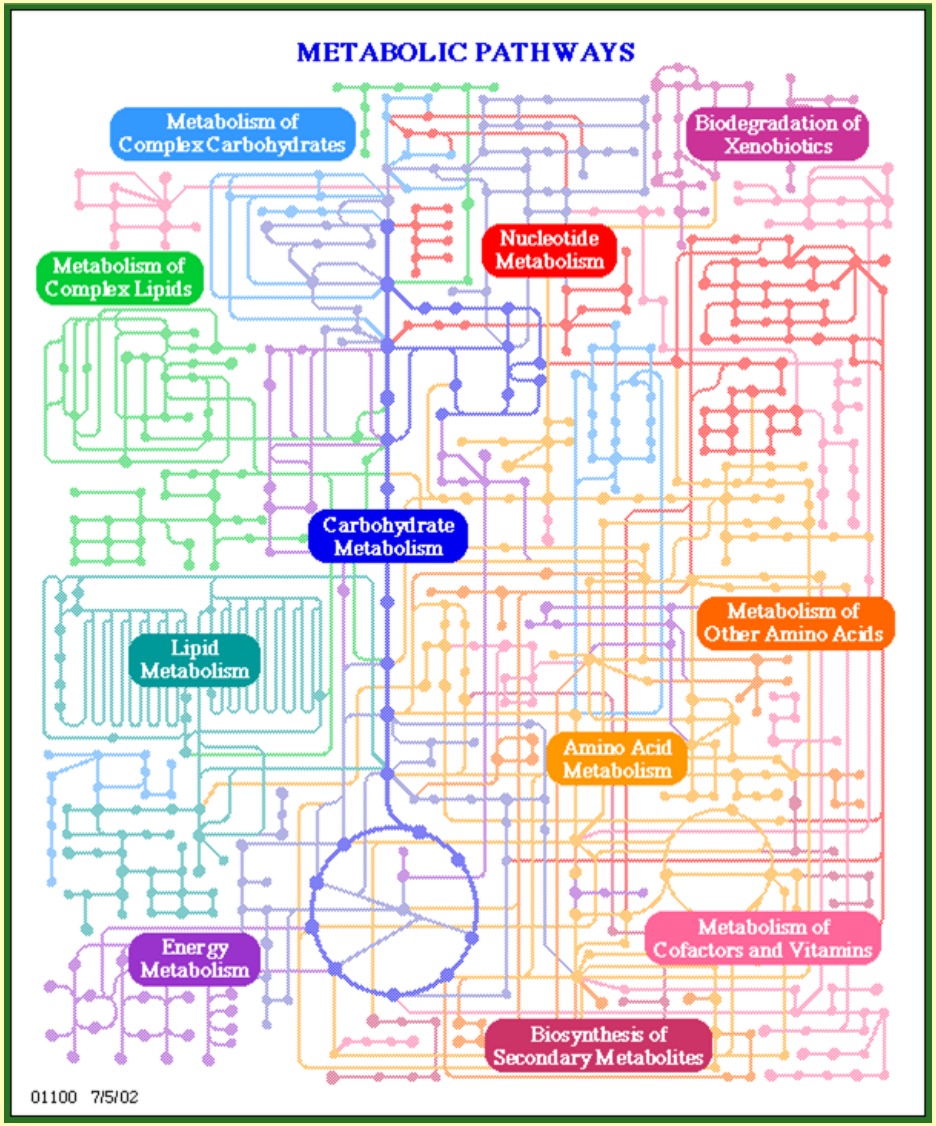
Structural Proteins

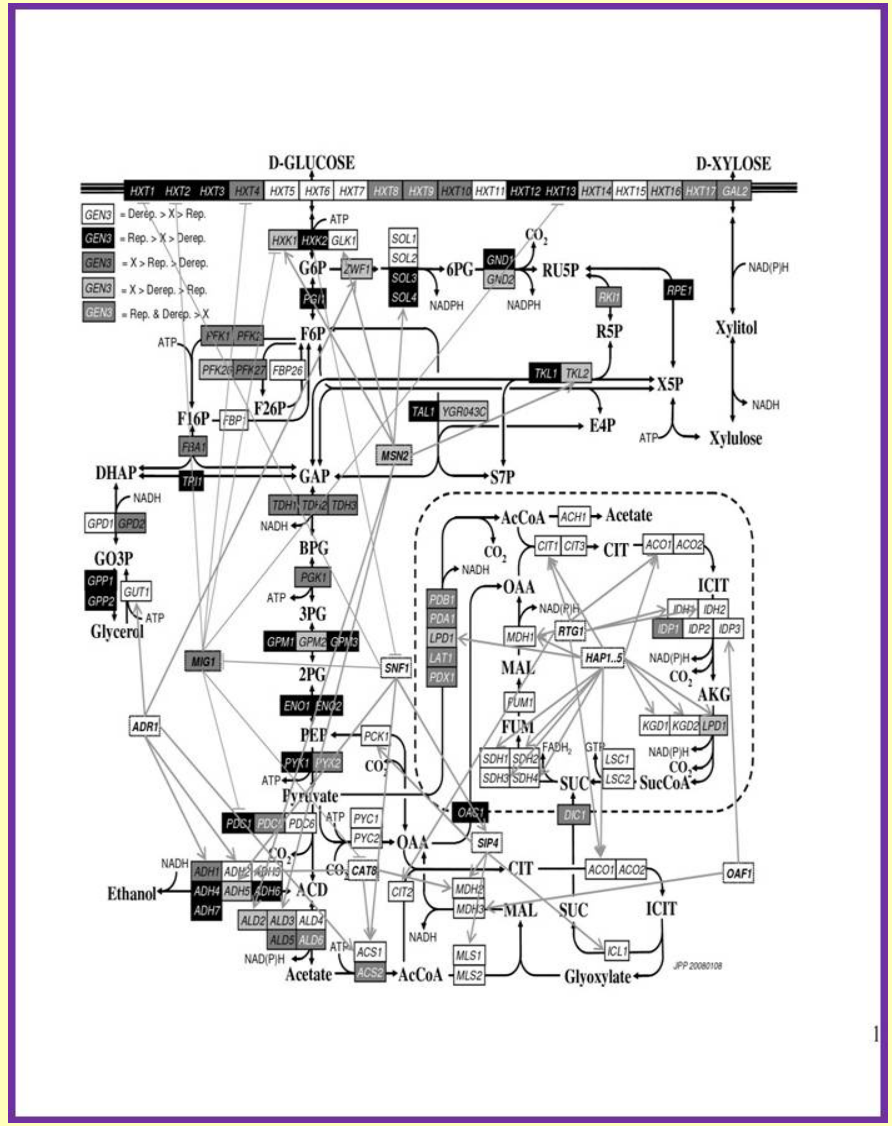


Signal Transducing Proteins



Catalytic & regulatory & signal transducing proteins of metabolic networks





Stages of development

Development is very complicated multistage biological process. It begins by fertilization and zygote formation and reaches its end by creation of a fully developed viable fetus.

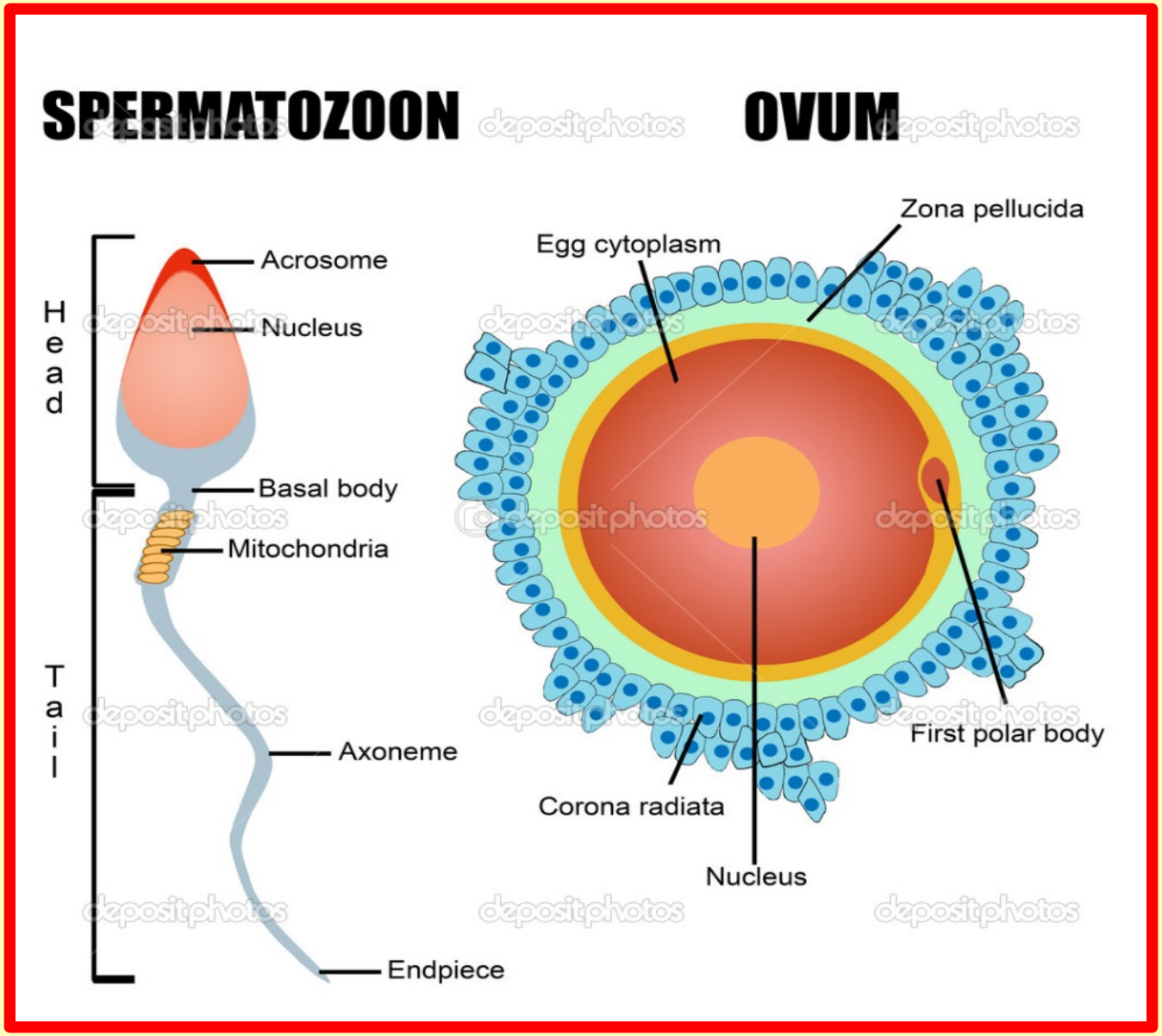
Though this definition is literally accepted within the context of traditional genetics, it does not reflect the fact that development is an ever continuing process that persists all through the life span of the organism. However, according to this traditional concept, development, basically, comprises the following stages:

1. Fertilization and early post-fertilization genomic alterations.

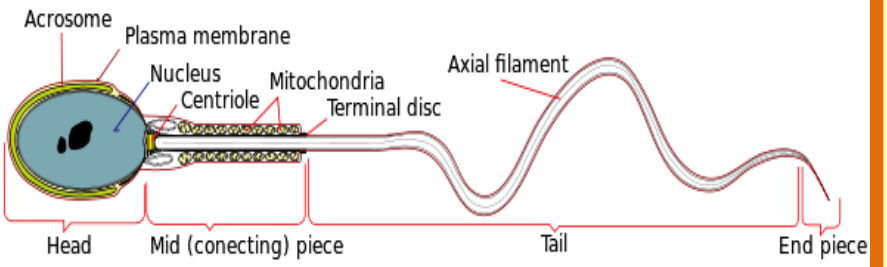
2. Cell division (cleavage) and multiplication, differentiation, specialization, localization, migration, and apoptosis.

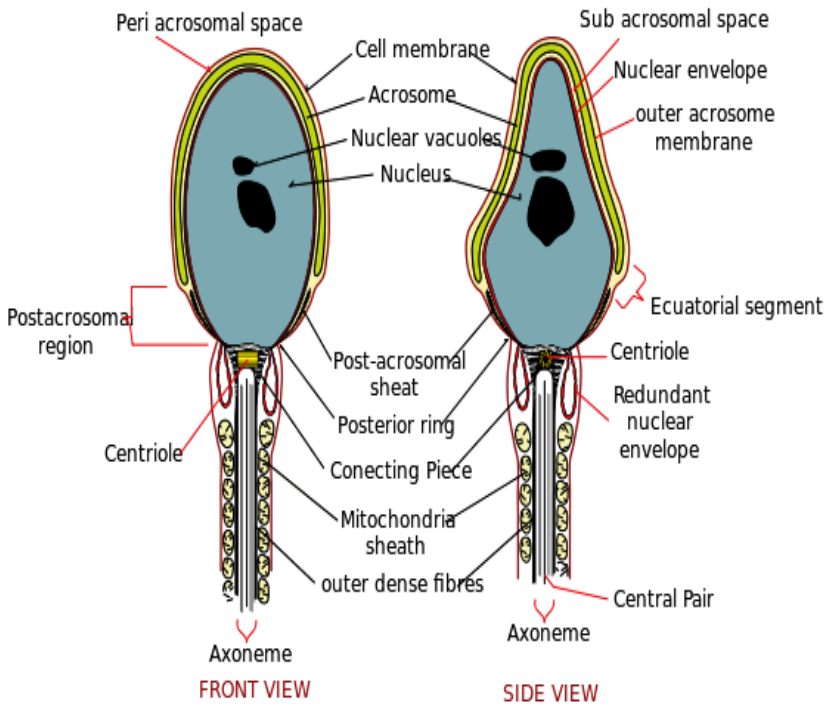
3. Morphogenesis of specialized tissues (histogenesis) and organs (organogenesis) in accordance with the predefined species-specific genetically-determined programmed pattern (patterning) and position (positioning) of all anatomical parts and landmarks of the developing embryo (embryogenesis).

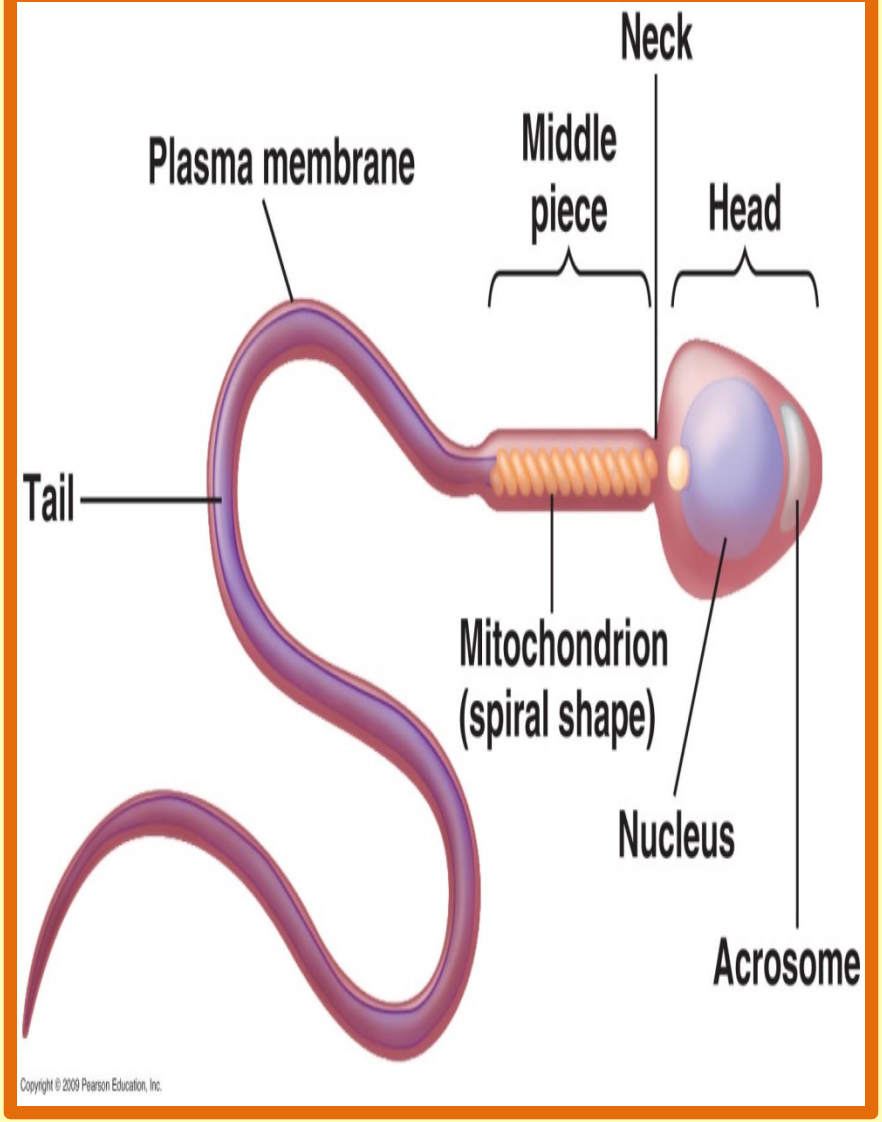
Human Gametes



Human Sperm


Acrosome
Plasma membrane
Nucleus
Centriole
Mitochondria
Terminal disc
Axial filament
Head
Mid (conecting) piece
Tail
End piece


Peri acrosomal space
Cell membrane
Acrosome
Nuclear vacuoles
Nucleus
Sub acrosomal space
Nuclear envelope
outer acrosome membrane
Postacrosomal region
Post-acrosomal sheat
Posterior ring
Conecting Piece
Mitochondria sheath
outer dense fibres
Centriole
Axoneme
FRONT VIEW
Ecuatorial segment
Centriole
Redundant nuclear envelope
Central Pair
Axoneme
SIDE VIEW


Neck
Plasma membrane
Middle piece
Head
Tail
Mitochondrion (spiral shape)
Nucleus
Acrosome
Copyright © 2009 Pearson Education, Inc.

Fertilization accomplishes two separate biological activities: sex determination of the developing fetus and start of development. It comprises many events: contact and recognition between sperm and ovum, regulation of sperm entry into the egg, fusion of genetic material from the two gametes and activation of ovum metabolism to start development.

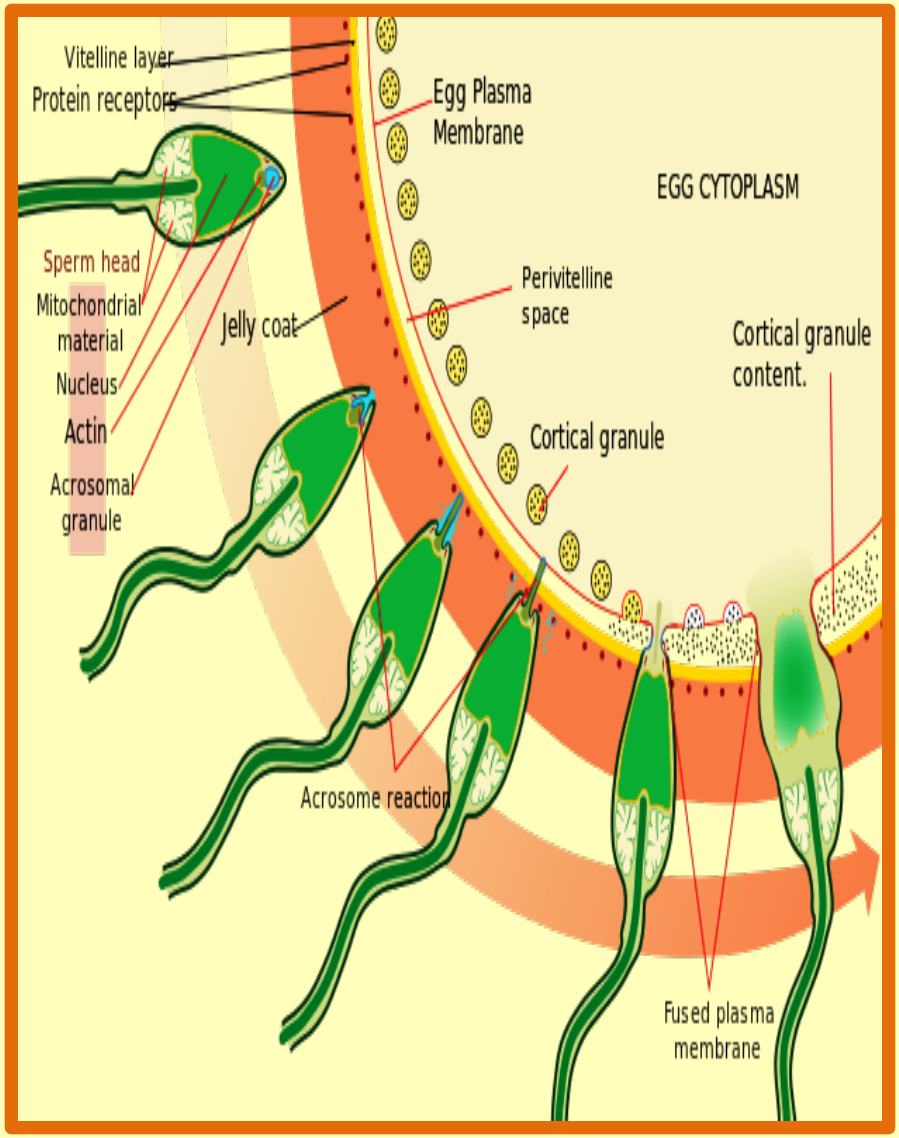
The sperm head consists of a haploid nucleus and the acrosome which is derived from the Golgi apparatus and contains enzymes needed to digest extracellular membranes surrounding the ovum. The neck of the sperm contains the mitochondria and the centriole that generates the microtubules of the tail. Energy for tail motion comes from mitochondrial ATP and a dynein ATPase in the tail.
The ovum contains a haploid nucleus, haploid polar body and a cytoplasm full of ribosomes, mRNAs, proteins, large collections of dense cortical granules containing large amounts of calcium and

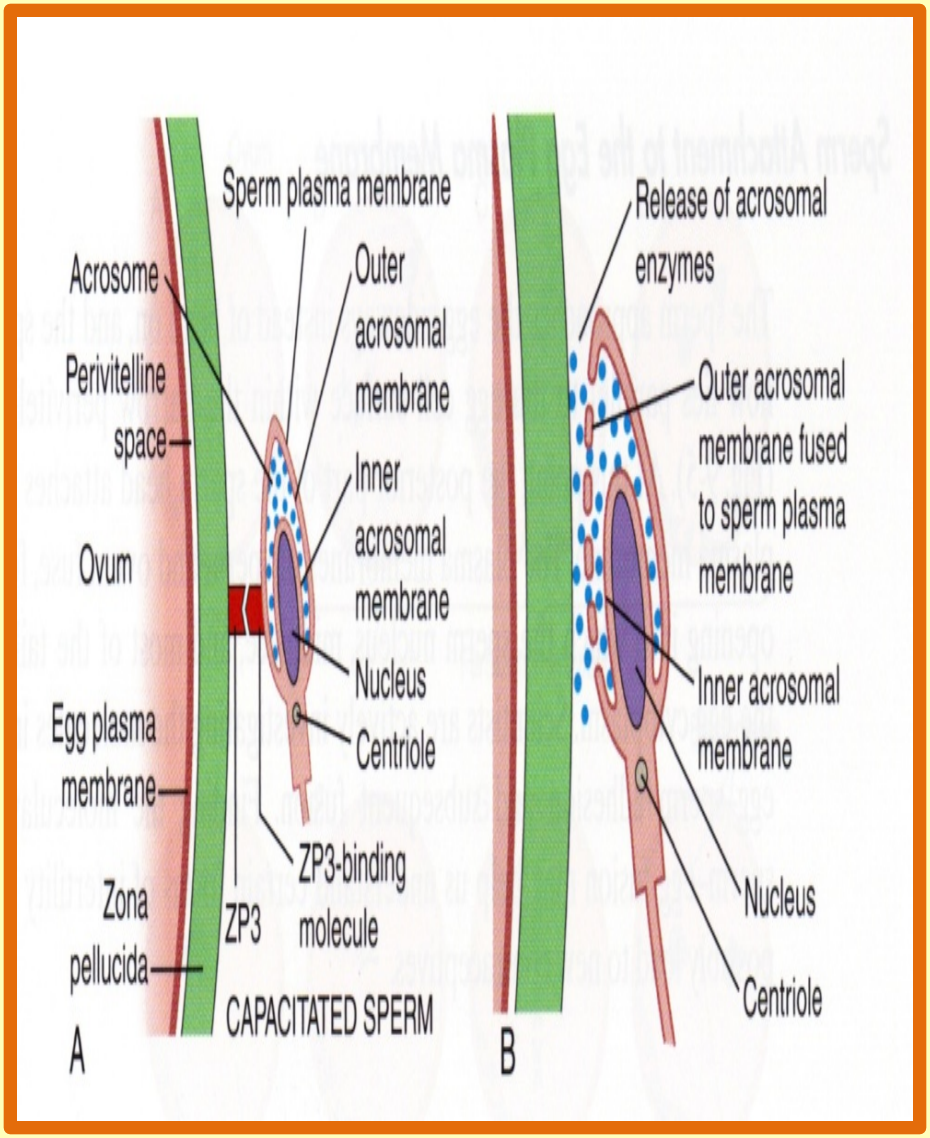
lying beneath the plasma membrane and nutritive proteins. Other mRNAs and proteins used as morphogenetic regulatory factors are also stored in the ovum. The plasma membrane of the ovum is surrounded by an extracellular layer, the zona pellucida, used in sperm recognition.

After binding to the zona pellucida, the sperm must be capacitated by the acrosome reaction in the female reproductive tract before they are capable of fertilizing the ovum. The acrosome reaction is initiated on the zona pellucida by compounds in the ovum wherein the acrosomal vesicle undergoes exocytosis to release its enzymes.

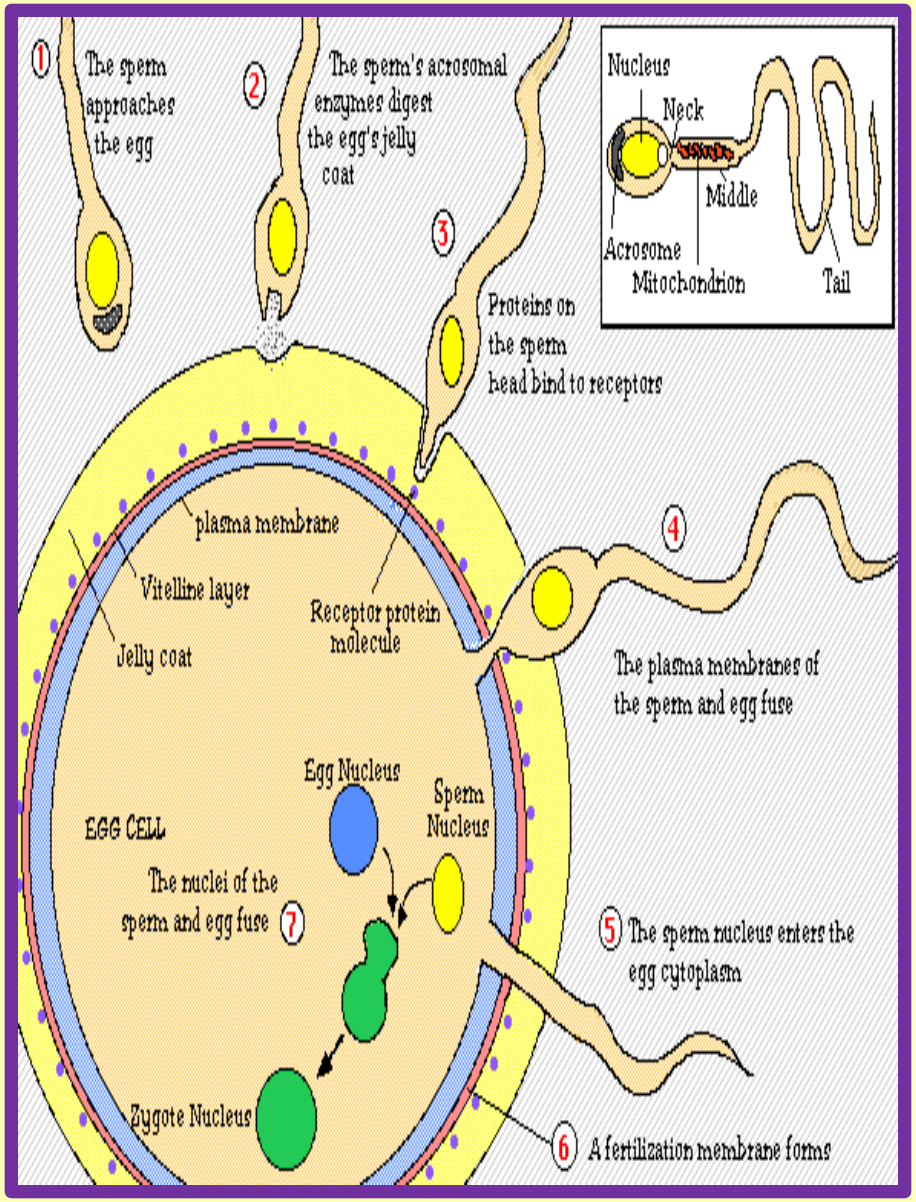
Fusion between sperm and ovum follows the penetration of the zona pellucida and is mediated by protein molecules that merge sperm and ovum plasma membranes by binding fertilin proteins in

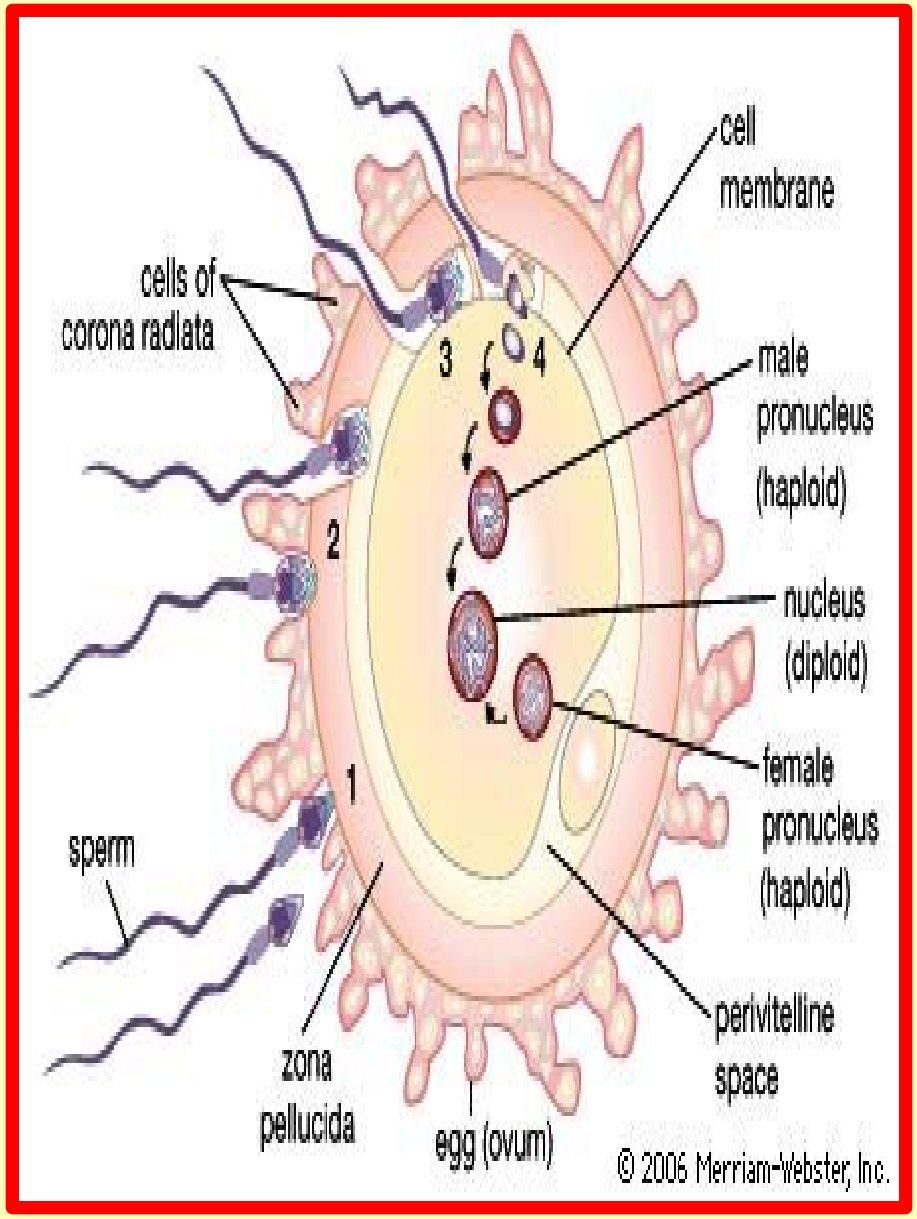
Fertilization





Fertilization and Zygote formation

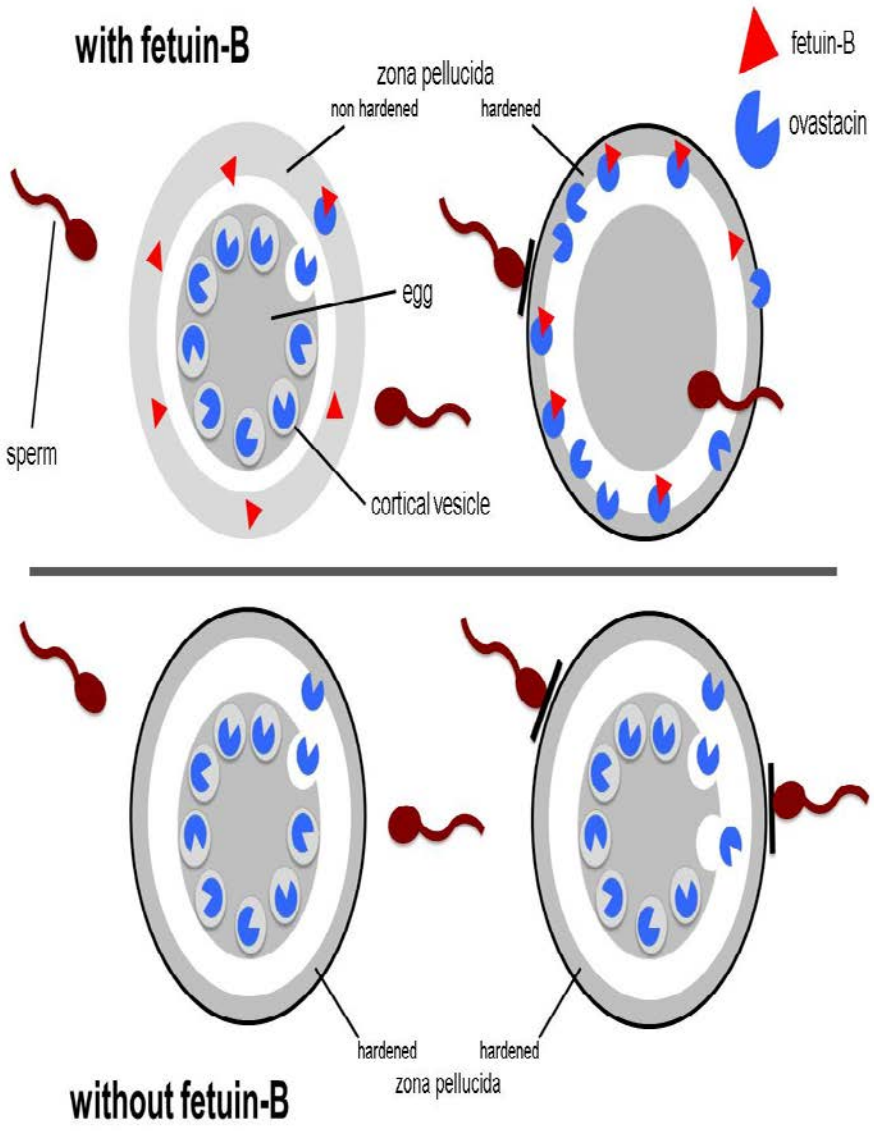


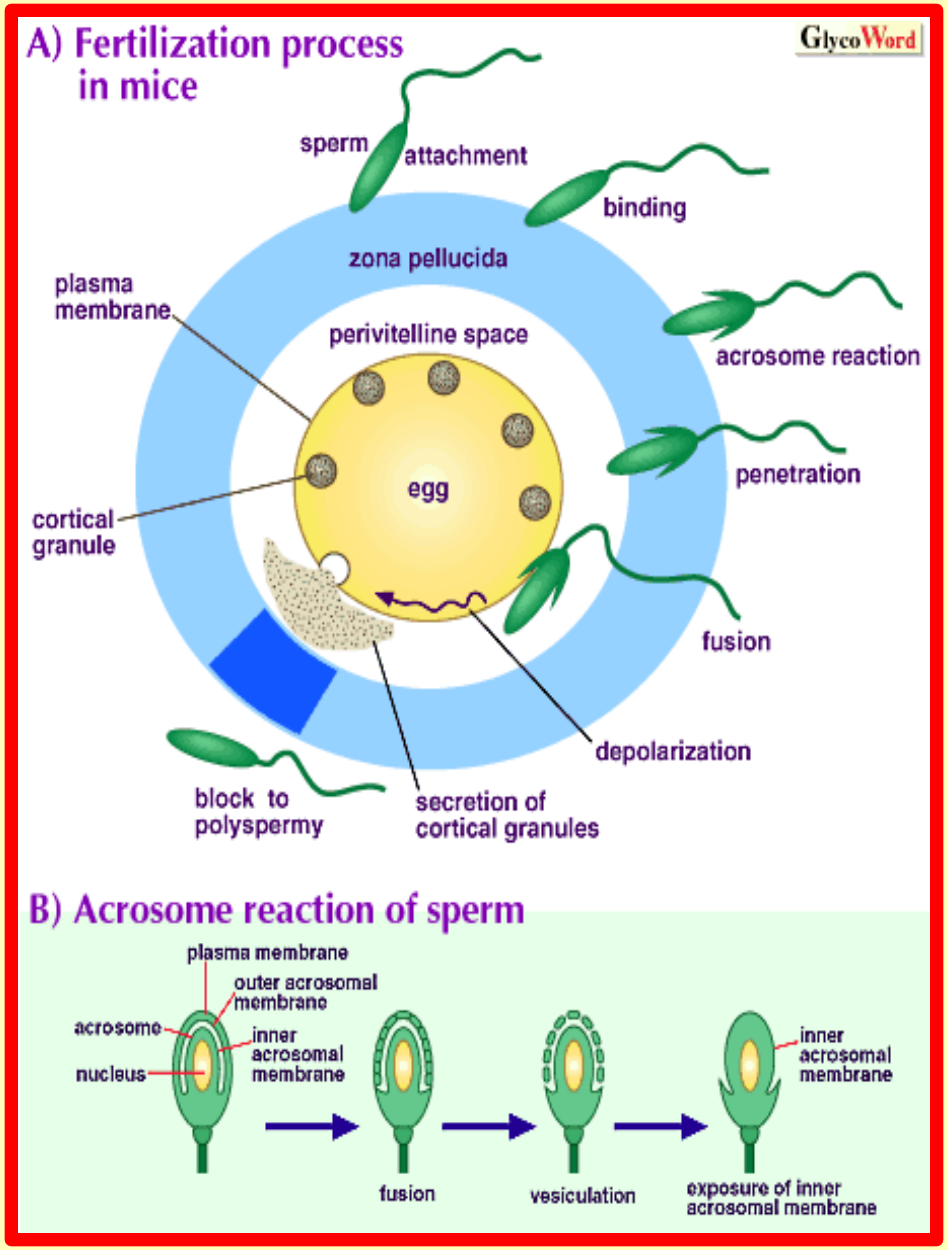


the sperm to integrin proteins in the ovum.

Polyspermy results when two or more sperms can penetrate and fertilize the ovum. Polyspermy is usually lethal due to the resulting genomic imbalance, since it results in existence and fusion of three sets (triploid) or even four sets (tetraploid) of chromosomes in the developing zygote. There are two precautionary mechanisms that block polyspermy. A fast electrical block mediated by sodium ions causing rise of the resting potential of the ovum membrane leading to blocking of fusion of the sperm with the ovum. The second blocking mechanism is a slow physical barrier mediated by calcium ions. A flood of calcium ions propagates from the point of sperm entry causing the cortical granules to fuse with the ovum cell membrane. The released contents of the granules cause the stroma of the zona pellucida to harden the membrane envelope and sperms can no longer bind to or penetrate the zona.

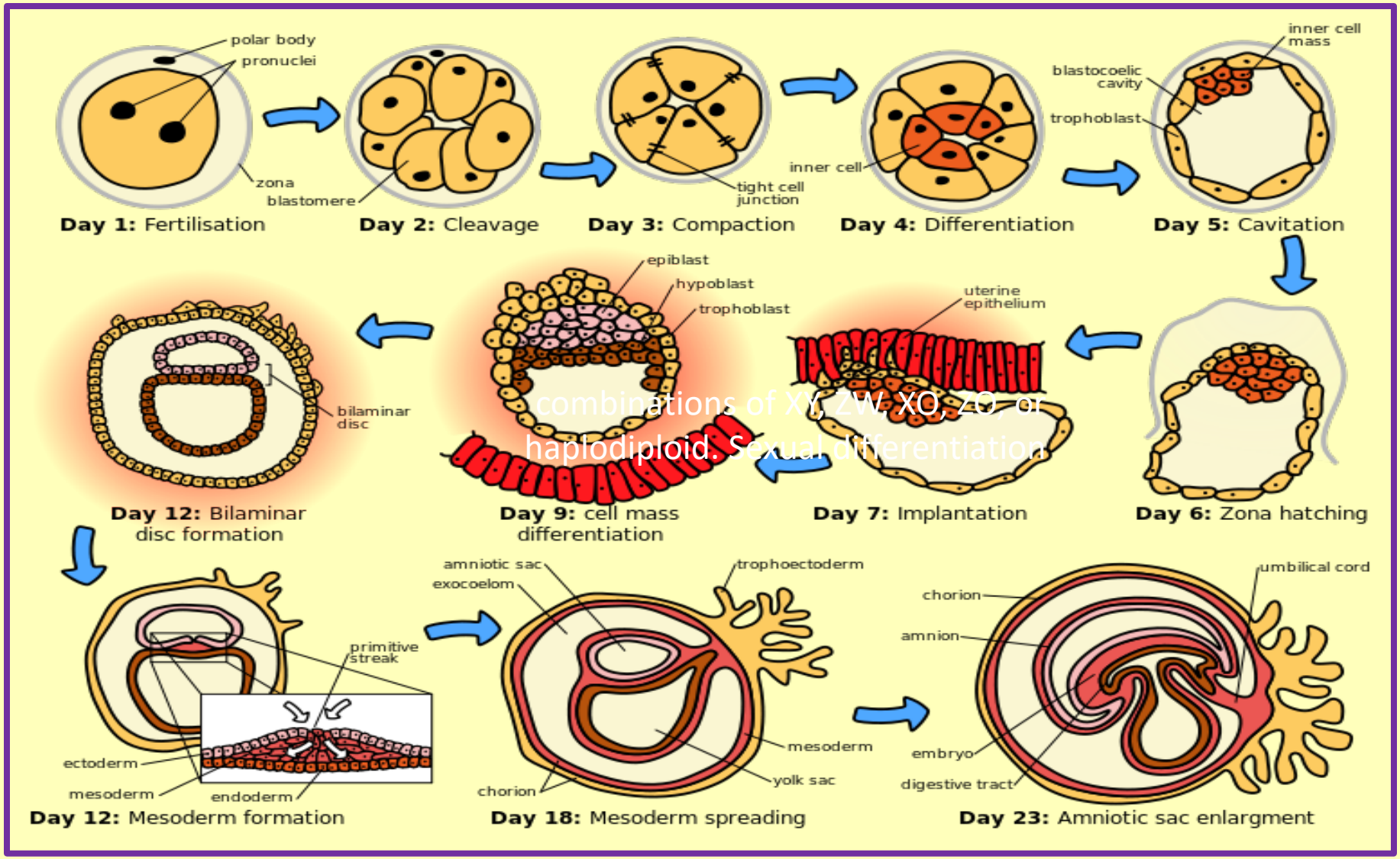
Regulation of Polyspermy





Following fertilization, the male pronucleus and the female pronucleus migrate toward each other, the pronuclei disintegrate and their chromosomes gather around a common metaphase plate. In mammals, the genome of the ovum shows maximum expressive activity immediately following fusion with the genome of the sperm which remains repressed for nearly the first few (4-5) post-fertilization days. This state of genomic imprinting of the sperm genome has no clear explanation and disturbances in this pattern of differential genomic expression can lead to arrest of development or aborted abnormal development at very early stages.

Human Embryogenesis – Early Steps



combinations of XY, ZW, XO, ZO, or haplodiploid. Sexual differentiation

From Wikipedia, the free encyclopedia

Sex determination in humans

Parameters of sex determination of humans

1. Genic sex.
2. Chromosomal sex.
3. Gonadal sex.
4. Internal genital sex.
5. External genital sex.
6. Hormonal sex.
7. Biochemical sex.
8. Psychological sex.
9. Phenotypic sex.

1. In humans, primary sex determination (determination of gonadal sex) is a function of the sex chromosomes where XX individuals are females and XY individuals are males.

2. The Y chromosome plays a key role in male sex determination. XY and XX mammals both have a bipotential gonad that makes the primary sex cords. In XY males, these cords continue to be formed within the gonad and eventually differentiate into Sertoli cells of the testes and the interstitial mesenchymal cells of the cords become the Leydig cells.

3. In XX females, the internal sex cords undergo degeneration, and a second set of cortical sex cords are formed. These new cords remain on the periphery of the gonad. Though the germ cells enter the sex cords they are not released from the gonad until puberty. The epithelium of the sex cords becomes the granulosa cells and the mesenchyme becomes the thecal cells.

4. The *SRY* gene is the major testis-determining factor and is located on the Y chromosome. It encodes the synthesis of a DNA-binding protein that is thought to compete with the *DAX1*

protein. It is thought that if SRY is produced in large amounts, it activates (either directly or indirectly) the *SF1* gene and inhibits the *WNT4* gene.

5. The SF1 gene product is believed to activate the SOX9 gene, as well as several other genes involved in synthesis of both steroid hormones and anti-Müllerian duct hormone (AMH). SOX9 may organize the genital ridge epithelium to form testes, but the corresponding ovary-forming genes have not yet been found, although the WNT-4 gene may be important in this regard.

6. Secondary sex determination in humans involves the hormones produced by the developing gonads. In females, under estrogenic stimulation, the Müllerian duct differentiates into the oviducts, uterus, cervix, and upper portion of the vagina. In males, the Müllerian duct is destroyed by the AMH produced by the Sertoli cells, while the testosterone produced by the Leydig cells enables

the Wolffian duct to differentiate into the vas deferens and seminal vesicles. In females, the Wolffian duct degenerates because of the lack of the effects of testosterone. Conversion of testosterone to dihydrotestosterone in the genital rudiment and prostate gland precursor enables the differentiation of the penis, scrotum, and prostate gland, and Individuals with mutations of genes encoding these hormones or their receptors may have a distinction between their primary and secondary sex characteristics.

Sex determination of the developing embryo is accomplished once fertilization is completed. This signifies the crucial importance of this process since it has far reaching effects on development due to the marked differences of the chromosomal constitution between male and female embryos and the resulting differential responses to developmental morphogenetic effectors between both sexes.

Biological systems of sex determination

A. Genetic sex-determination systems

Chromosomal determination

1. XX/XY sex chromosomes system
2. XX/X0 sex chromosomes system
3. The X-only (XO) sex chromosomes system
4. ZW/ZZ sex chromosomes system
5. U/V sex chromosomes system
6. Haplodiploidy sex determination system.

B. Non-genetic sex-determination systems

1. Temperature-dependent sex determination
2. Sex reversal system
3. Biochemically induced sex determination system
4. Other sex-determination systems

a. Parthenogenesis

b. Hermaphroditism

c. Sexual–asexual reproductive systems.

d. Infection-dependent sex determination.

A. Genetic Sex Determination Systems

1. The XX/XY sex-determination system

This is the most familiar sex determination system as it is found in humans. In this system, females have two sex chromosome (XX) of the same kind while males have two distinct sex chromosomes (XY). The X and Y sex chromosomes are different in shape and size from each other, unlike the autosomes, and are termed allosomes. Humans and many species have a gene (SRY) gene located on the Y chromosome that determines maleness, others (such as the fruit fly) use the presence of two X chromosomes to determine femaleness.

2. The XX/X0 sex determination system

In this variant of sex determination systems, females have two copies of the sex chromosome (XX) but males have only one (X0). The 0 denotes the absence of a second sex chromosome. Generally in this method, sex is determined by amount of genes expressed

across the two chromosomes. This system is observed in a number of insects, including the grasshoppers, crickets and in cockroaches.

3. The X-only or XO sex determination system

A small number of mammals, e.g. the spiny rat, lack a Y chromosome. In this system, both genders lack a second sex chromosome. The mechanism of XO sex determination is not yet understood.

4. ZW/ZZ sex chromosomes system

The ZW sex-determination system is found in birds, some reptiles, and some insects and some other organisms. It is the reverse of the XX/XY system since females have two chromosomes of different kinds (ZW) and males have two of the same kind of chromosomes (ZZ).

5. U/V sex chromosomes system

In some Bryophyte and some algae species, the gametophyte stage of the life cycle rather than being hermaphrodite occurs as separate male or female individuals that produce male and female gametes

respectively. When meiosis occurs in the sporophyte generation of their life cycle, the sex chromosomes known as U and V assort in spores that carry either the U chromosome only (U) and give rise to female gametophytes or the V chromosome only (V) and give rise to male gametophytes.

6. Haplodiploidy sex determination system

Haplodiploidy is found in insects belonging to Hymenoptera, such as ants and bees. Unfertilized eggs develop into haploid individuals which are the males. Diploid individuals are generally female but may be sterile males. Males cannot have sons or fathers.

Most females in the Hymenoptera order can decide the sex of their offspring by holding received sperm in their spermatheca and either release them into their oviduct to begin fertilization or keep them till they degrade. This allows the control of number of workers depending on the status and needs of the colony.

B. Non-genetic sex determination systems.

1. Temperature-dependent sex determination (TSD)

In some species of reptiles, including alligators, some turtles and the tuatara, sex is determined by the temperature at which the egg is incubated during a temperature-sensitive period.

For some species, sex determination is achieved by exposure to hotter temperatures resulting in the offspring being one sex and cooler temperatures resulting in the other. For others species using TSD, it is exposure to temperatures on both extremes that results in offspring of one sex, and exposure to moderate temperatures that results in offspring of the opposite sex. These systems are known as Pattern I and Pattern II, respectively. The specific temperature required to produce each sex are known as the female-promoting temperature and the male-promoting temperature.

Some species do not have the SRY gene and their TSD system is based on other genes, such as DAX1, DMRT1, and SOX9, that are

expressed or not expressed depending on the temperature. Their expression leads to synthesis of specific enzymes necessary for sex determination of the developing organism.

However, the sex of some of these species, such as the Nile Tilapia, Australian skink lizard and Australian dragon lizard is initially determined by chromosomes but can later be changed by the temperature of incubation of the hatching eggs.

2. Sex reversal system

Some species such as some snails practice developmental reversal or change of their sex where adults start out as males then become females.

3. Biochemically induced sex determination system

In some species, e.g. the marine worm (Bonellia viridis), larvae become males if they get in physical contact with a female, and develop as females if they end up on the bare sea floor. This is triggered by the presence of a sex-determining enzyme (bonellin) synthesised by female worms.

4. Other sex-determination systems

a. Parthenogenesis

A few species of fish, amphibians, reptiles, and insects reproduce by parthenogenesis and are female altogether.

b. Hermaphroditism

Some species, e.g. common earthworm and certain species of snails, have no sex-determination system and develop as hermaphrodites.

c. Sexual–asexual reproductive systems

Some reptiles, such as the boa constrictor and komodo dragon can reproduce both sexually and asexually depending on whether a mate is available or not.

d. Infection-dependent sex determination

In some arthropods, sex is determined by infection with a specific bactertia of the genus Wolbachia, where infected individuals have a ZZ chromosomal constitution and develop entirely as males. The exact mechanism of sex chromosome determination due to the effect of infection is not yet known.

Biological systems of sex determination

Sex determination system	Male	Female
1. XX/XY sex chromosomes system	XY	XX
2. XX/X0 sex chromosomes system	X	XX
3. The X-only (XO) sex chromosomes system	X	X
4. ZW/ZZ sex chromosomes system	ZZ	ZW
5. U/V sex chromosomes system	V	U
6. Haplodiploidy sex determination system	Haplodiploid	Diploid

Stages of Development

Embryonic development in mammals progresses along four major consequent stages:

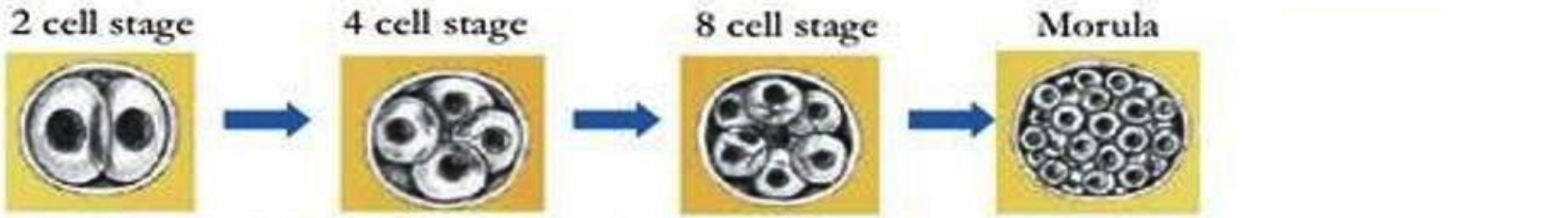
1. Cleavage
2. Patterning
3. Differentiation
4. Growth

1. Cleavage

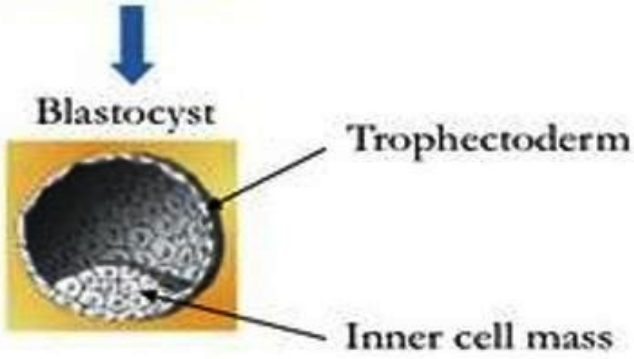
Mitosis and cytokinesis of the zygote produces an increasing number of smaller cells, each with an exact copy of the genome present in the zygote. However, the genes of the zygote are not expressed at first. The early activities of cleavage are controlled by the mother's genome that is by mRNAs and proteins she deposited in the unfertilized egg. In humans, the switch-over occurs after 4–8 cells have been produced. Cleavage ends with the formation of a blastula.

Stages of cleavage

Cleavage (days 1-6)



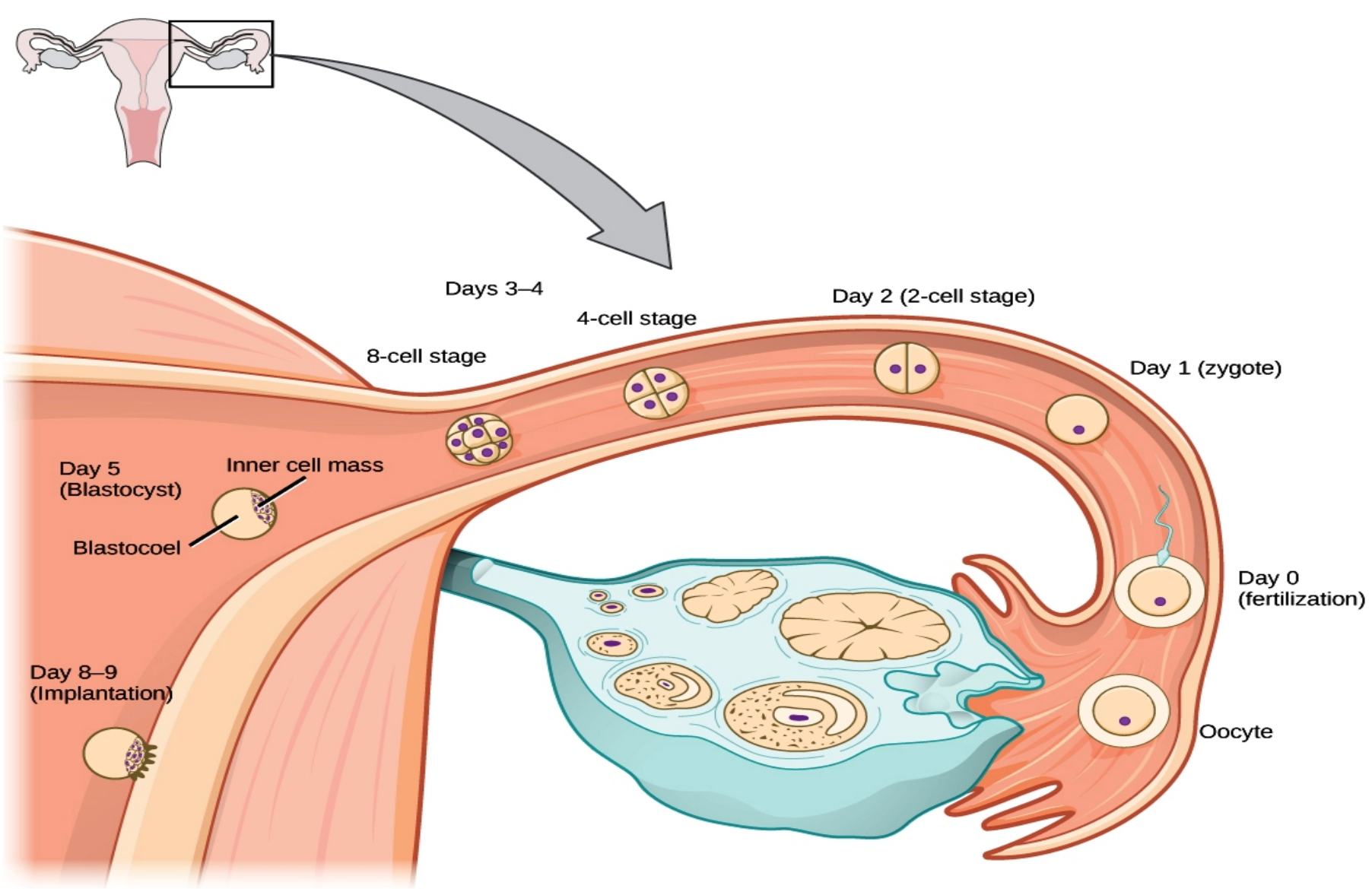
1. Zygote divides into two cells
2. Day two: morula (Latin for mulberry)
3. Cell signaling begins
4. Embryo begins to organize
5. Blastocyst forms on days 4-6
6. Two parts of blastocyst
   - Trophectoderm (placenta, amnion)
   - Inner cell mass (embryo)
7. Size is 0.1 mm



Once fertilization has occurred, the zygote begins to undergo a series of mitotic cleavages until after 2-3 days it generates a ball of cells called the **morula** because of its resemblance to a mulberry. The mammalian mitotic cleavages are the slowest in the animal kingdom, occurring 12-24 hours apart. During the process of cell division, the morula moves along the uterine Fallopian tubes until it arrives in the uterine cavity, which is engorged and ready for its implantation. The morula undergoes selective apoptotic processes and progresses to a cyst-containing mass called the **blastocyst (immature ball sac)** that contains two types of cells:

A. An **external cell layer** that becomes the **trophoblast.** The cells of this layer are the first cell type that undergo **differentiation** in the developing embryo. Trophoblast cells adhere to, and invade, the uterine endometrium to implant the embryo in the uterus. They eventually give rise to the embryonic portion of the **placenta** that feeds the embryo in utero during development.

Timeline of fertilization and implantation



B. The internal cell layer, also called the inner cell mass (ICM), that gives rise to the embryo proper and the associated yolk sac, allantois and amnion. If the ICM cells, or blastomeres, are removed from the blastocyst and grown in culture, these cells divide and become embryonic stem cells (ES cells). The inner cell mass or ES cells are able to produce all tissues of the embryo proper. However, they cannot generate trophoblast cells. Therefore, these cells are pluripotent. ES cells can be grown indefinitely in an undifferentiated state and retain their pluripotency after prolonged culture.

2. Patterning

During this phase, cells produced by cleavage organize themselves in layers and masses, a process called gastrulation, and the pattern of the main configuration of the future organism appears as:

1. Front end to rear end (anterior-posterior axis)
2. Back surface and belly surface (dorsal-ventral axis)
3. Left side and right side (side to side axis)
4. Proximal and distal patterning.

There is little visible differentiation of the cells in the various layers, but probes for cell-specific proteins reveal that different groups of cells have already started on specific paths of future development.

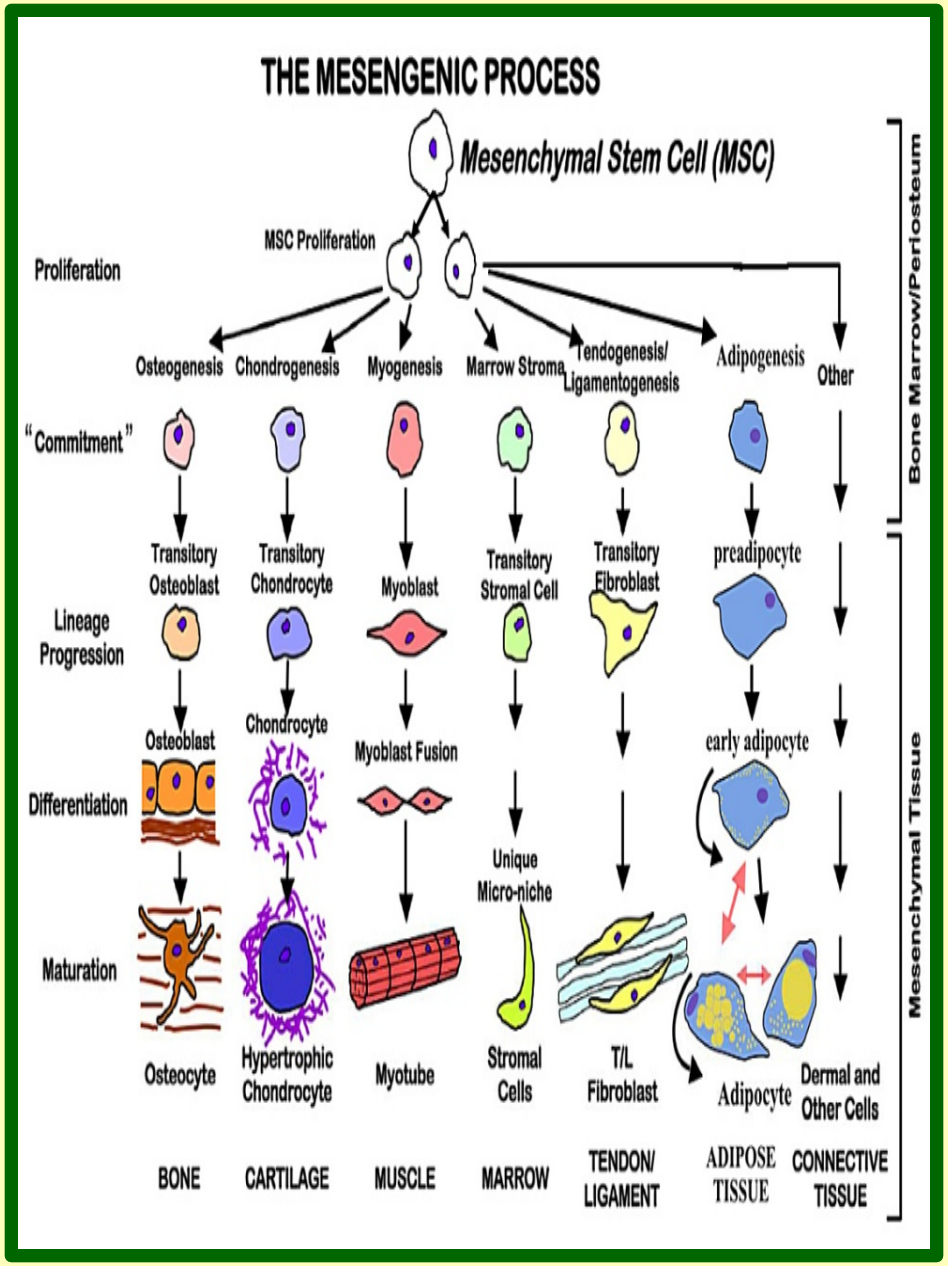
Gastrulation signifies full expressive capacity of the cells and results in formation of the three major germ layers: the ectoderm, the mesoderm and the endoderm.

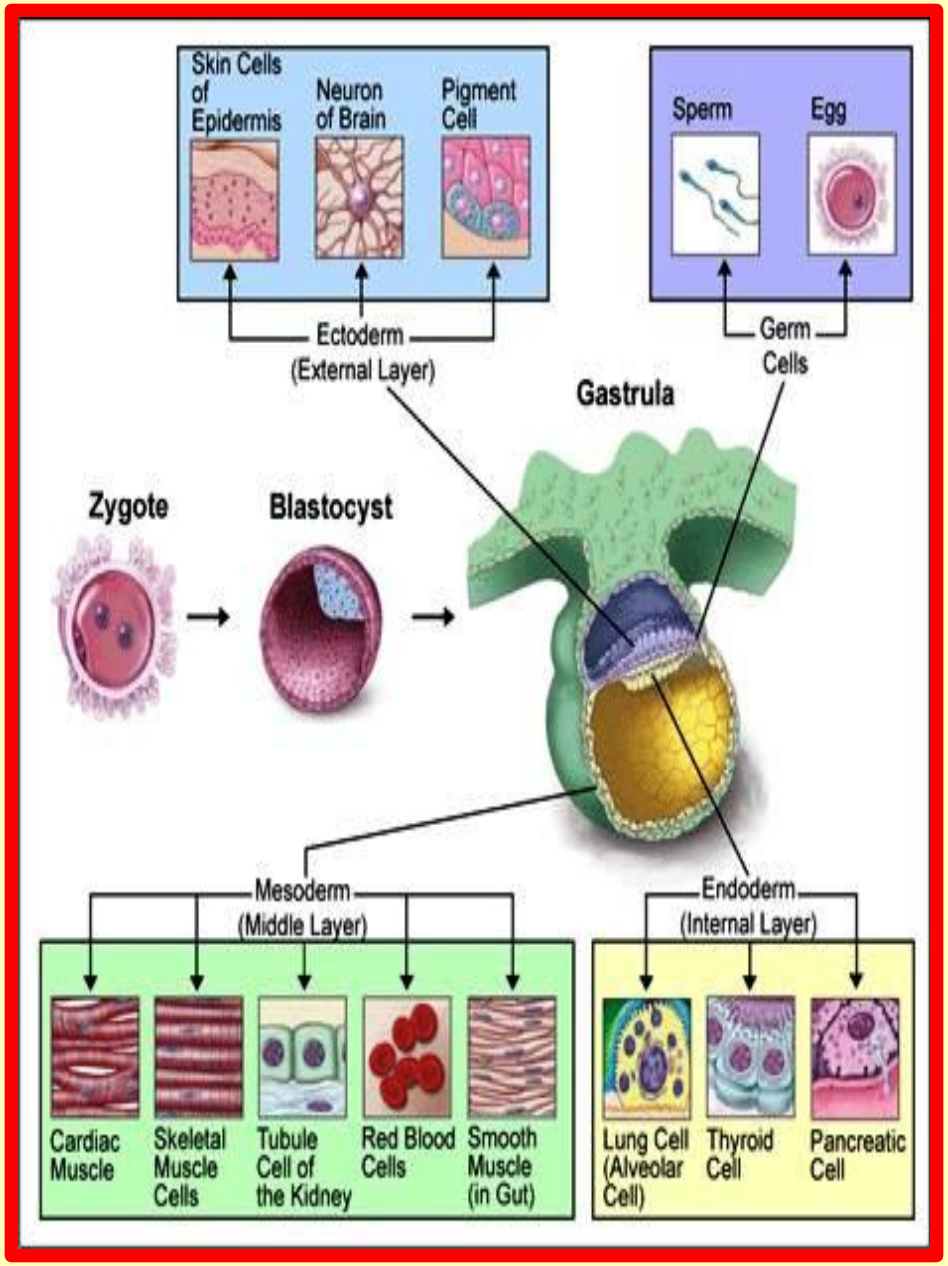
3. Differentiation

In time, the cells of the embryo differentiate to form the specialized structures and functions that they will have in the adult. They form neurons, blood cells, skin cells, muscle cells, etc. These are organized into tissues, the tissues into organs, the organs into systems.

Major factors controlling and regulating differentiation include all aspects of genetic imprinting. **Temporal imprinting** regulates the exact time limits of differentiation and specialization of every type of cells. **Spacial imprinting** regulates the cell-tissue-organ specific limits of localization within the wide context of the developing embryo/fetus. **Parental imprinting** regulates the differentiation and specialization of sex determining cells-tissues-organs of the developing fetus.

Differentiation and Specialization





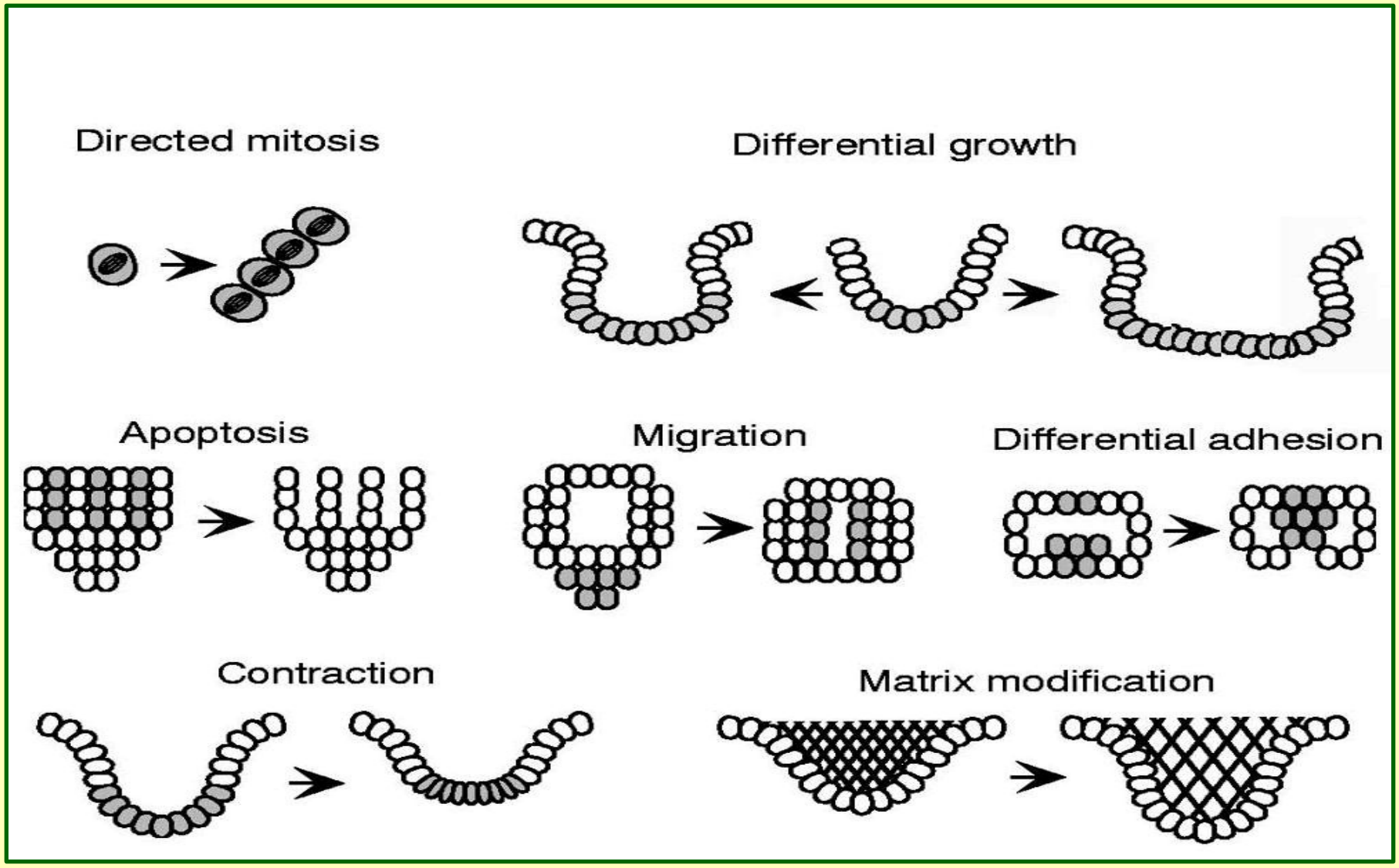
4. Growth

After all the body systems of the developing organism are formed, most species go through a period of growth. Growth occurs by the formation of new cells and more extracellular matrix.

Growth entails progressive quantitative increments in developed organs. On cell level, it comprises increase in size (**hypertrophy**) and in number as well (**hyperplasia**).

Growth is an ever continuing biological process all through the life cycle of the cell as well as the organism. However, relative decrease in growth potentials occur with time due to consequences of aging and senescence of dividing mother cells being transmitted to daughter cells.

Morphogenetic mechanisms

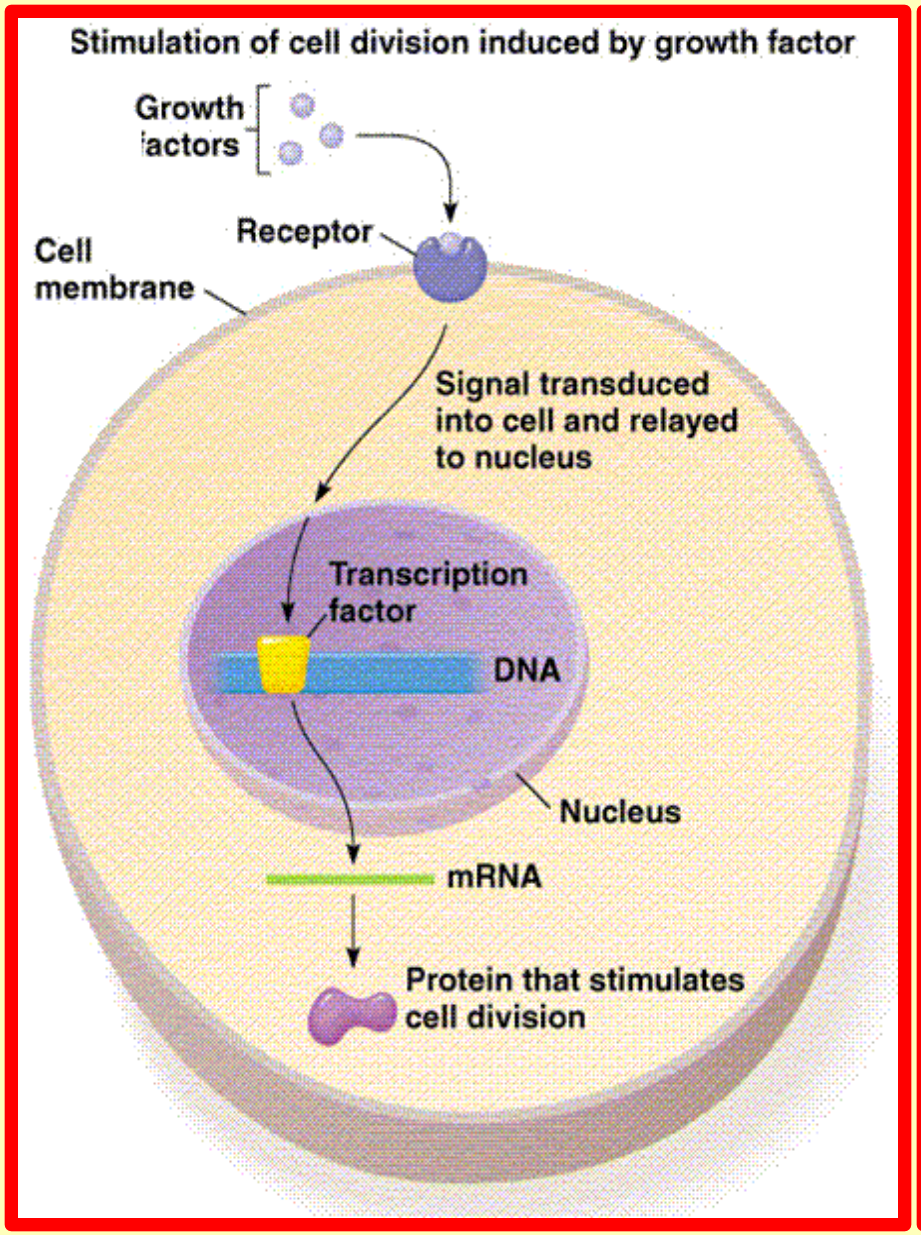


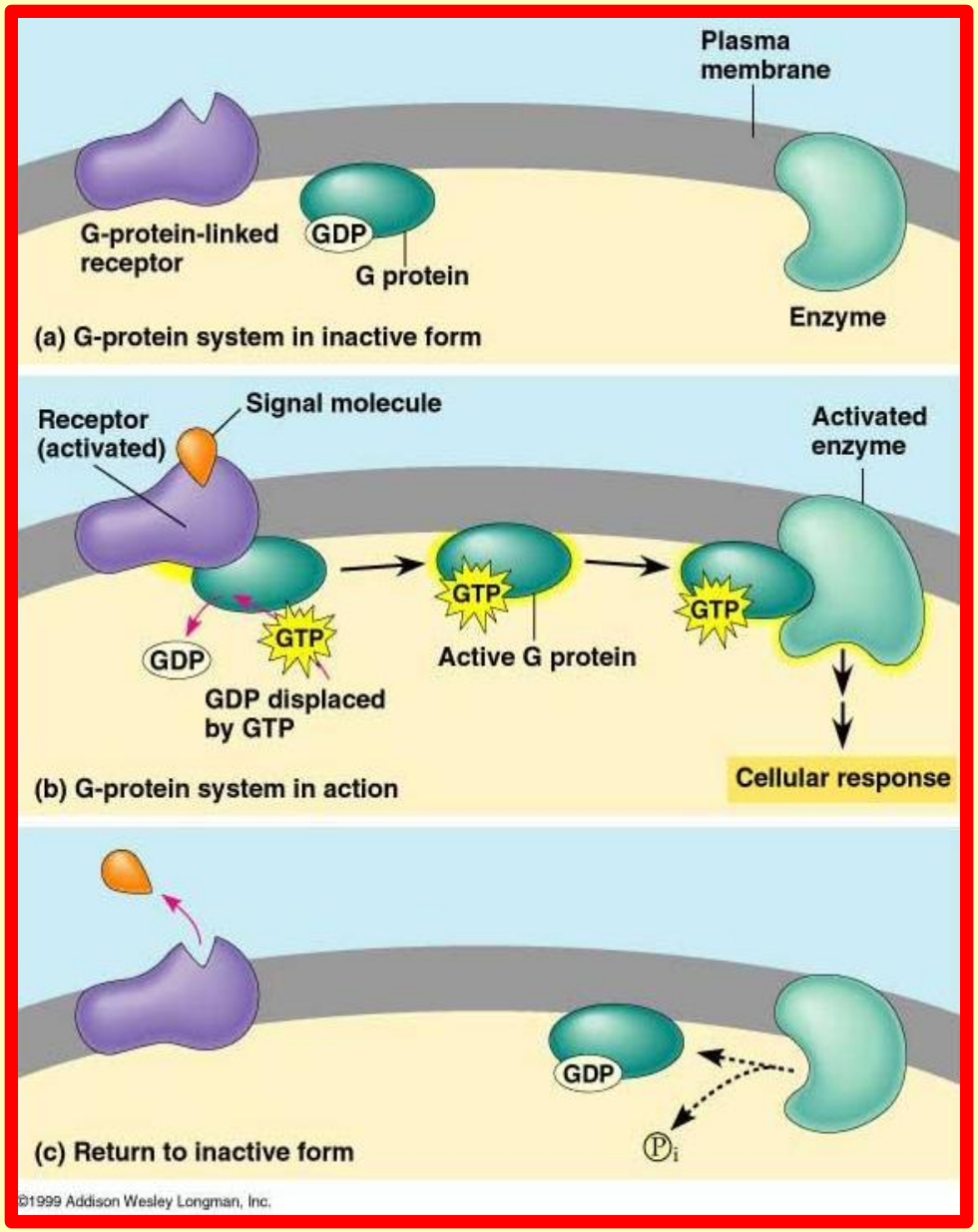
Signal transduction and signal pathways

Cell–cell interactions via signal-transduction pathways are crucial in the coordination of embryonic development. Typically, signalling pathways are activated by the binding of a specific ligand to a transmembrane receptor which in turn leads to the modification of cytoplasmic transducers. Subsequently, these transducers activate transcription factors that ultimately alter gene expression resulting in differential transcription of activated genes.

One of the most surprising findings about signalling processes is that only a few pathways are involved in and are responsible for most of embryonic development. These comprise seven major pathways: the wingless related (Wnt), transforming growth factor-β (TGF-β), Hedgehog (Hh), receptor tyrosine kinase (RTK), Janus kinase (JAK)/signal transducer and activator of transcription (STAT), Notch and nuclear receptor pathways.

Mechanisms of signal transduction





These pathways have been shown to act repeatedly during development and they are diverse with regard to their biochemical mechanisms and the complexity of the individual components that are involved. What these pathways have in common is the activation of specific target genes by the regulation of signal-dependent transcription factors. In the case of the Wnt, Notch, Hh and nuclear receptor signalling pathways, the signal-dependent transcription factors function as repressors in the absence of signalling, but turn into activators on ligand signalling.

Mechanisms of signal transduction

The specificity of cellular responses can be achieved by at least five mechanisms, which in some cases act in combination, highlighting the network properties of signalling pathways in living cells.

1. The same receptor can activate different intracellular transducers in different tissues.

2. Differences in the kinetics of the ligand or the receptor might generate distinct cellular outcomes.
3. Combinatorial activation by signalling pathways might result in the regulation of specific genes. Several signalling pathways can be integrated either at signalling proteins or at enhancers of target genes.
4. Cells that express distinct transcription factors might respond differently when exposed to the same signals.
5. compartmentalization of the signal in the cell can contribute to specificity. The recruitment of components into protein complexes prevents cross signalling between unrelated signalling molecules or targets multifunctional molecules to specific functions.

Developmental signaling pathways

1. The Wnt signaling pathways are a group of signal transduction pathways composed of proteins that pass signals from outside of a cell through cell surface receptors to the inside of the cell.

Three distinct Wnt signaling pathways have been characterized: the canonical Wnt pathway, the non-canonical planar cell polarity pathway, and the non-canonical Wnt/calcium pathway. All three Wnt signaling pathways are activated by the binding of a Wnt-protein ligand to a receptor on the cell surface (Frizzled family receptor) which passes the biological signal to a receptor protein (Dishevelled protein) inside the cell.

The canonical Wnt pathway is mainly involved in regulation of transcription of genes and the non-canonical planar cell polarity pathway regulates the architecture of the cell cytoskeleton that is responsible for the shape of the cell while the non-canonical Wnt-

calcium pathway regulates calcium homeostasis inside the cell. Wnt signal transduction pathways are highly conserved since they have similar structures and functions across many species from fruit flies to humans.

Wnt signaling was first identified for its role in carcinogenesis, but has since been recognized for its critical regulatory functions in embryonic development. The embryonic processes it controls include body axis patterning, cell fate specification, cell proliferation, and cell migration. These processes are necessary for proper formation of important tissues including bone, heart, and muscle.

The clinical importance of this pathway has been demonstrated by mutations that lead to a variety of diseases, including breast and prostate cancer, glioblastoma, type II diabetes, and many others.

2. The hedgehog signaling pathway constitutes a critical signaling regulatory pathway during development of all known animals. In the embryo, it regulates morphogenesis of a variety of tissues and organs. Hedgehog proteins are essential regulators of a variety of critical developmental processes including growth, patterning and morphogenesis. In adults, they control proliferation of stem cells.

There are three human hedgehog (HH) proteins: Sonic hedgehog, Desert hedgehog and indian hedgehog. Each of them is encoded by a different gene and expressed at different times of development in specific cell types. They are tightly controlled by highly complex, yet divergent, transcriptional enhancers and suppressor species of miRNAs. The release, diffusion and binding of these proteins to the transmembrane domain proteins is controlled by various other proteins including Skinny hedgehog (Sit), Dispatched (Disp), Tout-velu (Ttv) and Hedgehog-interacting protein (Hip).

Aberrant activation of the HH pathway has been linked to multiple types of human cancer particularly basal cell carcinoma. Disruption of HH signaling during embryonic development, either through genetic mutations or maternal teratogen consumption, leads to a wide spectrum of severe developmental disorders such as holoprosencephaly.

a. Sonic hedgehog protein (SHH)

This signal transducing protein plays key roles in regulating vertebrate organogenesis, such as growth of digits on limbs and organization of the brain. Sonic hedgehog protein is encoded by SHH gene located on long arm of chromosome 7, is a critical morphogen, i.e. a molecule that diffuses to form a concentration gradient and has different effects on the cells of the developing embryo depending on its concentration. Mutations of the SHH gene are the leading causes of holoprosencephaly and other midline cerebral defects. SHH remains important in the adult since it controls cell division of adult stem cells and has been implicated in development of some cancers.

b. Desert hedgehog protein (DHH)

This regulatory signal transducing protein is encoded by the DHH gene located on the long arm of chromosome 12. Defects in this protein have been associated with partial gonadal dysgenesis (PGD) accompanied by mini-fascicular polyneuropathy. This protein may be involved in both male gonadal differentiation and perineurial development.

c. Indian hedgehog protein (IHH)

This protein is encoded by the IHH gene located on the long arm of chromosome 2. It specifically plays a major regulatory role in bone growth and differentiation and is involved in regulating the differentiation, proliferation and maturation of chondrocyte especially during stage of endochondral ossification. Its effects are regulated by feedback control of a parathyroid hormone-related peptide (PTHrP). Known mutations in this gene are linked to many developmental bone malformations including brachydactyly type A1 and acro-capito-femoral dysplasia.

3. The Notch signaling pathway

The notch signaling pathway is a highly conserved cell signaling system present in most multicellular organisms. Notch is present in all metazoans, and mammals possess four different notch receptors, referred to as NOTCH1, NOTCH2, NOTCH3, and NOTCH4. The notch receptor is a single-pass transmembrane receptor protein.

This signaling pathway is important for cell-cell communication, which involves gene regulation mechanisms that control multiple cell differentiation processes during embryonic and adult life. Notch signaling also has a role in the following processes:

1. Neuronal function and development.
2. Stabilization of arterial endothelial and angiogenesis.
3. Regulation of many processes of myocardial formation, crucial cell communication events between endocardium and myocardium during the formation of the valve primordial and ventricular development and differentiation and cardiac valve homeostasis.

4. Timely cell lineage specification of both endocrine and exocrine pancreas.
5. Binary fate decisions of gut cells to drive cell differentiation along either the secretory or the absorptive functional lineage.
6. Expansion of the hematopoietic stem cell compartment during bone development and commitment to the osteoblastic lineage.
7. Expansion of the hemogenic endothelial cells along with signaling axis involving Hedgehog signaling pathway.
8. T cell lineage commitment from common lymphoid precursor.
9. Regulation of cell-fate decision in mammary glands at several distinct development stages.
10. Control of the actin cytoskeleton through the tyrosine kinase.
11. Notch signaling is required in the regulation of polarity and mutation experiments have shown that loss of Notch signaling causes abnormal anterior-posterior polarity in somites.
12. Notch signaling plays an important regulatory role during body left-right asymmetry determination in vertebrates.

Notch signaling pathway has been found to be dysregulated in many cancers, and faulty notch signaling is implicated in many diseases including T-cell acute lymphoblastic leukemia, Tetralogy of Fallot, Multiple Sclerosis, Alagille syndrome, Cerebral Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy, and many other disease states.

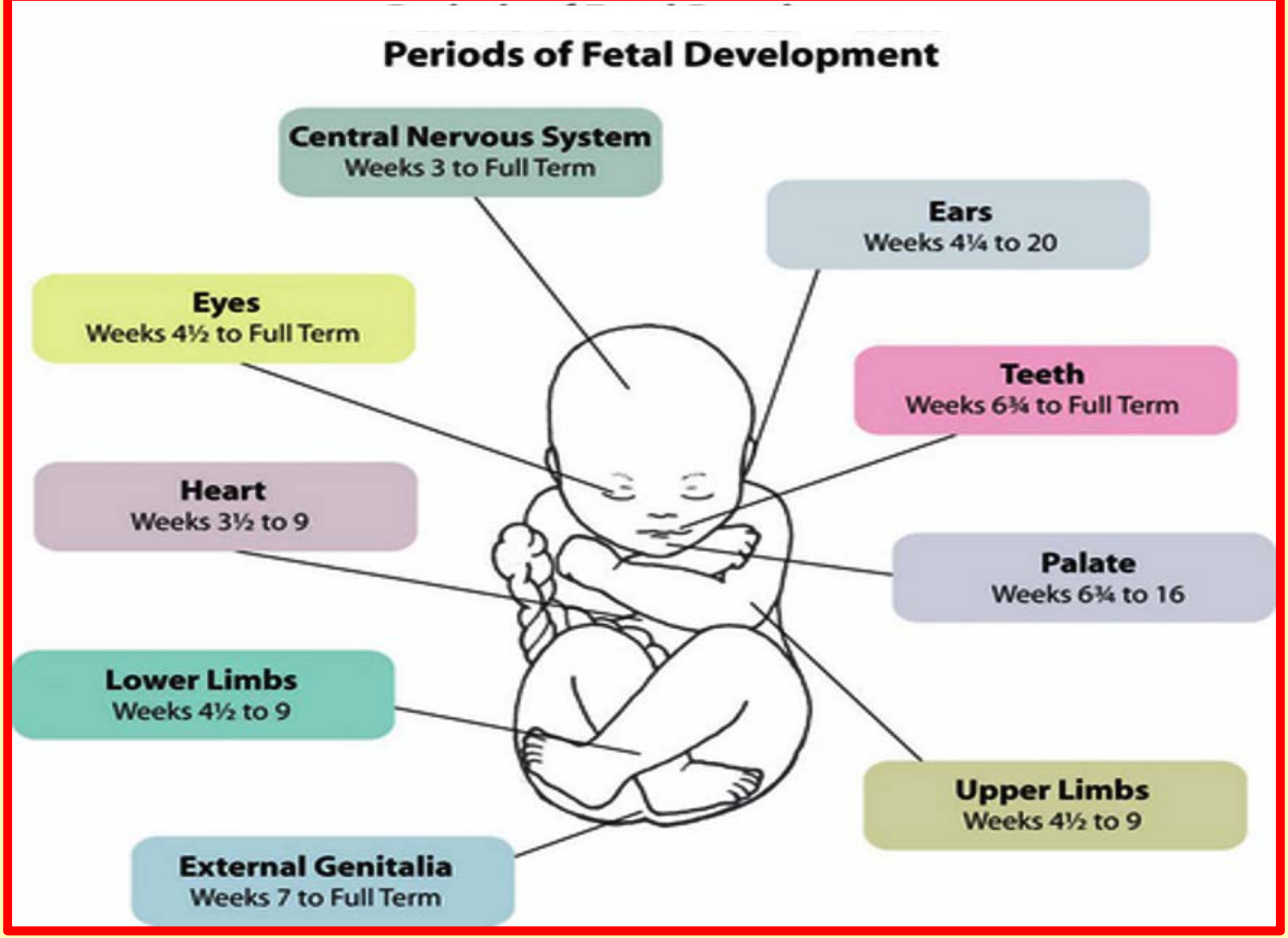
Notch signaling in adult brain function

In addition to its multiple developmental functions, Notch pathway proteins and ligands are persistently expressed in cells of the adult nervous system, suggesting a role in CNS plasticity throughout life. Experimentally induced animal mutations results in deficits in spatial learning and memory. Dysregulation of Notch proteins in post-natal life due to mutations of the genes encoding Notch proteins probably underlies the neurodegenerative manifestations of many neurological and cognitive disorders including Alzheimer disease and presenile dementias.

4. The fibroblast growth factor signaling pathway

The fibroblast growth factors (FGFs) represent one of the relatively few families of extracellular signaling peptides that have pivotal key regulatory role in metazoan development. FGFs are required for multiple processes in both protostome and deuterostome groups. Given the wide range of regulatory roles attributed to the FGFs, it is perhaps not surprising that mis-regulation of this signalling pathway has been implicated in a number of human disease conditions.

Periods of Fetal Development



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